BP Control Better With Combination Therapy

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Fixed-dose combination therapy increased blood pressure control rates from 37% to 76% over 18 months in patients with high-risk hypertension in an ongoing large, multinational trial reported at the annual meeting of the American Society of Hypertension.

Control rates were even higher in the U.S. cohort, where 80.5% of patients achieved control to less than 140 mm Hg—an unprecedented rate for a U.S. trial, reported Dr. Kenneth Jamerson, who presented interim results from the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. Significant reductions in systolic blood pressure were seen across all patient populations, including African Americans.

Dr. Jamerson and associates randomized 11,463 patients age 55 years or older with a systolic blood pressure of at least 160 mm Hg or currently on antihypertensive therapy to treatment with either Lotrel, which contains the ACE inhibitor benazepril and the calcium-channel blocker amlodipine, or to benazepril plus the diuretic hydrochlorothiazide (HCTZ).

The study data support 'broadening the use of combination therapy as an initial therapy.'

DR. JAMERSON

At 18 months, patients achieved an average decline in blood pressure from 145/80 mm Hg to 132/74 mm Hg. Almost one-fifth of patients went on to achieve a systolic BP of less than 120 mm Hg. The study remains blinded, so blood pressure reductions were not stratified based on treatment. Cardiovascular morbidity and mortality outcomes, the study's primary end point, are anticipated after the trial ends in 2008.

Dr. Jamerson thinks this data will help shift the traditional approach to hypertension management in which clinicians initiate monotherapy, then add medications as needed to achieve blood pressure goals.

"We think we provide substantial evidence to suggest that initial combination therapy is very effective, and think there is substantial evidence here to support broadening the use of combination therapy as an initial therapy," said Dr. Jamerson, professor in the department of internal medicine, division of cardiovascular medicine, University of Michigan, Ann Arbor.

Although 97% of patients in the study were already taking antihypertensive medication, just 37.5% had their blood pressure controlled at baseline to 140/90 mm Hg—the currently recommended target in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Dosages were titrated at month 2 to a fixed dose of benazepril 40 mg/amlodipine 10 mg or benazepril 40 mg/HCTZ 25 mg, with the option of adding other antihypertensive agents at month 3. Overall, 35% of patients used add-on medications, said Dr. Jamerson, who has received grant/research support from Novartis, which sponsored the study and markets Lotrel.

At 18 months, the average systolic BP declined from 153 mm Hg to 137 mm Hg in Nordic patients, from 142 mm Hg to 129 in the U.S. cohort, and from 145 mm Hg to 133 mm Hg in African Americans.

More work is needed among patients with diabetes and chronic kidney disease, Dr. Jamerson said. Their respective mean systolic BPs decreased from 145 mm Hg to 131.5 mm Hg and from 149 mm Hg to 136 mm Hg—both short of the JNC 7 goal of 130 mm Hg for these difficult-to-treat populations. Overall, 60% of ACCOMPLISH participants have diabetes, and had a BP control rate of 15%.

ASH president Dr. Suzanne Oparil said in an interview that these are the highest overall control rates ever achieved, but at roughly 80% are only slightly higher than the 65% reported in previous hypertension trials. The low systolic BP rates reported in the U.S. cohort may reflect higher values at baseline in the Nordic cohort and a more cautious treatment approach typically used by European physicians.

Dr. Oparil, professor of medicine, physiology, and biophysics at the University of Alabama, Birmingham, disagreed that these results will shift treatment patterns, as the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial already showed that controlling blood pressure quickly is important. "It's not that paradigm shifting because that's what we're preaching anyway," she said.

Some members of the audience suggested that the go-slow approach remains warranted in certain patients such as the elderly because of potential side effects including hypotension. Hypotension was reported in 207 or 2% of patients, and 0.4% of these were hospitalized for the condition. Dizziness was reported in 2,144 (19%) patients, peripheral edema in 2,009 (17.6%), and chest pain in 159 (1.4%).

Dr. Jamerson responded by noting that the average age of the ACCOMPLISH cohort was 68 years, but added that the final data will be analyzed to determine how many hypotensive events are drug related.

The study is powered to show that the combination of benazepril and amlodipine will reduce cardiovascular morbidity and mortality in patients with high-risk hypertension by 15%, compared with the combination of benazepril and HCTZ. Theoretical research suggests that a combination of ACE inhibitors and calcium-channel blockers might confer an additional benefit, as they have been shown independently to increase vascular nitric oxide production, Dr. Jamerson said. ■

PREPARE Trial Shows How to Safely Cut Back on ICD Shocks

BY BRUCE JANCIN
Denver Bureau

DENVER — Implantable cardioverter defibrillators can be programmed to safely eliminate three-quarters of unnecessary shocks in patients with a primary prevention indication for the device, according to a study presented at the annual scientific sessions of the Heart Rhythm Society.

The Primary Prevention Parameters Evaluation (PREPARE) was a prospective, nonrandomized, 38-center study involving 700 primary prevention patients with an implantable cardioverter defibrillator (ICD). Their single-chamber, dual-chamber, or biventricular ICDs were programmed to disregard supraventricular tachycardias and slow or nonsustained ventricular tachycardias (VTs) while aggressively expanding preferential use of antitachycardia pacing (ATP) to painlessly terminate fast VTs before resorting to maximum-energy shocks.

'Most of our ICD patients receive far too many shocks.'

DR. WILKOFF

The 691 historic controls drawn from two major clinical trials were primary prevention ICD patients for whom VT/VF (ventricular fibrillation) detection and treatment programming wasn't controlled, explained Dr. Bruce L. Wilkoff, lead investigator and director of cardiac pacing and tachyarrhythmia devices at the Cleveland Clinic Foundation.

The primary end point in PREPARE was the morbidity index, a composite of all spontaneous arrhythmias treated with shocks, instances of arrhythmic syncope, and untreated sustained symptomatic VT/VF episodes. During the first year of follow-up, the morbidity index was 0.18 events per patient-year in the PREPARE cohort and 0.69 events per patient-year in controls, for a highly significant 74% relative risk reduction. Of patients in the PREPARE cohort, 8% received a shock in the first year, compared with 18% of controls. Nine cases of arrhythmic syncope occurred in eight patients, with no injuries.

One-year mortality was 4.8% in the PREPARE group and 8.7% in controls, a difference that was nonsignificant in a multivariate analysis that controlled for potential confounders.

"I wasn't surprised to see we could reduce shocks. I was very pleased to see that there really was no big tradeoff" in terms of morbidity due to untreated arrhythmias, the electrophysiologist said.

Noting that most ICDs are implanted for primary prevention indications, Dr. Wilkoff said that "most of our ICD patients receive far too many shocks. … To me, every tachycardia terminated by ATP is a success, and those would all be inappropriate shocks [with conventional programming]. I can't see a reason not to do" the PREPARE programming, he added.

PREPARE programming included utilization of the ICD's built-in supraventricular tachycardia discrimination feature and detection of only those rhythms of at least 182 beats per minute and a duration of at least 30 of 40 ventricular beats. Pacing with ATP was programmed for episodes with a rate of 182-250 beats per minute, with a shock reserved for arrhythmias over 250 beats per minute and episodes not terminated by ATP.

Session cochair Dr. Hein J. Wellens called PREPARE "very impressive."

"The patient will be much happier with this approach. The other important point is that delaying shocks if you have a rapid VT apparently does not result in deterioration to VF. So there are all sorts of positive findings," observed Dr. Wellens, professor emeritus of cardiology at Maastricht (the Netherlands) University. He speculated that the observed mortality trend favoring PREPARE ICD programming might achieve significance with longer follow-up.

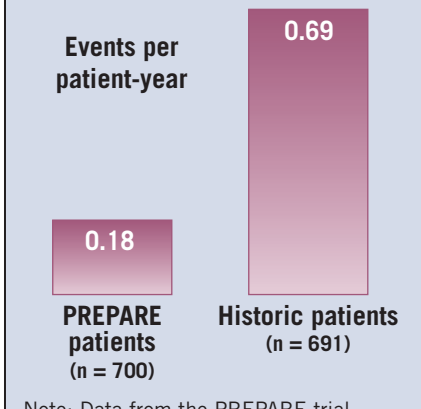
Dr. Wilkoff agreed that the data raise the possibility that inappropriate shocks for nonsustained arrhythmias might cause injury that promotes mortality. "It's a very intriguing idea, but this is not the study to prove that point," he said.

Heart Rhythm Society president Dr. Dwight W. Reynolds said in an interview that PREPARE has the potential for a large impact on practice. Some ICD physicians haven't been using ATP at all in primary prevention, and others have used it only for episodes with a maximum rate of 220 beats per minute.

"It's fairly strong encouragement to be much more aggressive with the ATP in the primary prevention setting," said Dr. Reynolds, professor of medicine and chief of the cardiovascular section at the University of Oklahoma, Oklahoma City.

Dr. Wilkoff is a consultant to Medtronic, which sponsored PREPARE. ■

ICD Programming to Reduce Shocks Lowered Morbidity Index



Note: Data from the PREPARE trial.
Source: Dr. Wilkoff

ELSEVIER GLOBAL MEDICAL NEWS