Drug Combo Reverses Left Ventricular Remodeling

BY DAMIAN McNAMARA
Miami Bureau

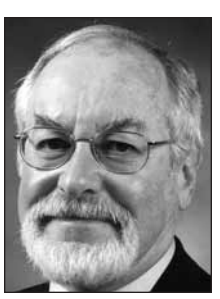
BOCA RATON, FLA. — Fixed-dose isosorbide dinitrate and hydralazine significantly reduces left ventricular volume and increases ejection fraction in African American patients with moderate to severe heart failure, according to a subanalysis of the African American Heart Failure Trial.

Decreases in brain natriuretic peptide corresponded with the 6-month improvements in cardiac remodeling.

In the African American Heart Failure Trial (A-HeFT), the drug combination (BiDil, Nitromed Inc.) was associated with an increase in survival of 43% for African Americans with moderate to severe heart failure (N. Engl. J. Med. 2004;351:2049-57). The magnitude of this finding surprised some because the A-HeFT patients were already aggressively treated for heart failure: 87% were already taking β-blockers, 78% were on ACE inhibitors, 39% were on aldosterone inhibitors, and 28% were taking angiotensin receptor blockers.

Regarding A-HeFT mortality, "the survival benefit versus placebo became obvious at 6 months or 7 months, and then the curves spread out remarkably after that," Jay N. Cohn, M.D., said during a late-breaking clinical trial session at the annual meeting of the Heart Failure Society of America.

Dr. Cohn and his associates performed a subanalysis of the A-HeFT data to determine whether improvements in left ventricular structure and function could explain the improvement in survival. They compared echocardiographic findings and blood brain natriuretic peptide (BNP) samples taken at baseline and after 6 months of treatment. One cardiologist evaluated all the digitized echocardiograms in blinded fashion.



Of the 1,050 self-identified African Americans enrolled in A-HeFT, 666 had ejection fraction values recorded at baseline and 6 months. Of this group, 329 were treated with combination therapy and 337 with placebo. In addition, there were 678 participants with left ventricular internal diameter in diastole (LVIDd) values taken at baseline and 6 months. Of this group, 337 were treated with the combination and 341 with placebo.

At 6 months there was a significant increase in ejection fraction in the combination group versus placebo, said Dr. Cohn, professor of medicine and director of the Rasmussen Center for Cardiovascular Disease Prevention at the University of Minnesota, Minneapolis. There was also a highly significant difference in LVIDd in the treatment group versus the placebo group, he added.

'I would be surprised if the ... remodeling is confined to the African American population.'

DR. COHN

A meeting attendee asked about possible variation with the measurements used in the study. "I'm more comfortable with the consistency of the LVIDd measurements, compared with the ejection fraction measurements, which can be interpreted differently," Dr. Cohn said.

The mean baseline BNP level was 300 pg/mL. By 6 months, the treatment group experienced a greater mean decrease (28 pg/mL), compared with the placebo group (11 pg/mL). Dr. Cohn called this a "striking difference between groups" that supports the cardiac remodeling improvements in the study.

Another meeting attendee asked how well the BNP values tracked with changes to left ventricular volume. "We don't know that yet, the tracking between the two is not always perfect," Dr. Cohn said. "BNP is not always perfect. BNP is a continuum, but the lower the better."

Another audience member asked Dr. Cohn if remodeling was dose dependent. "We haven't looked at that yet," he replied. "This is really the first look at these data." He and his associates plan to perform subgroup analyses in the future.

"I would be surprised if the benefit on remodeling is confined to the African American population," Dr. Cohn said. "We need to do that study."

"The combination of isosorbide dinitrate and hydralazine induces regression of left ventricular remodeling in patients already treated with neurohormonal inhibitors," Dr. Cohn concluded. "These data provide further support for the growing database that favorable effects on outcomes in heart failure can be attributed to favorable effects on left ventricular structural remodeling. ■

Cochrane Review Finds Use For Digoxin in Heart Failure

BY BRUCE JANCIN
Denver Bureau

VANCOUVER, B.C. — The latest Cochrane systematic review of digoxin for treatment of heart failure patients in sinus rhythm paints a picture of a more than 200-year-old drug that's still clinically useful, although it has no effect on mortality, William B. Hood Jr., M.D., said at a meeting sponsored by the International Academy of Cardiology.

"It's probably not first-line therapy. It's not very powerful. But it's available for patients who are not fully responsive to other agents that have become first-line treatments—the ACE inhibitors, β-blockers, spironolactone, and the angiotensin receptor blockers," added Dr. Hood, lead author of the recent Cochrane review and a cardiologist at the University of Washington, Seattle.

The metaanalysis was restricted to randomized, double-blind, placebo-controlled trials involving adults followed for at least 7 weeks. Thirteen trials totaling nearly 7,900 patients qualified, including the largest of all digoxin studies: the 6,800-patient, 3-year Digitalis Investigation Group (DIG) trial (N. Engl. J. Med. 1997;336:525-33).

Why even bother doing a metaanalysis when one trial is so dominant in size? Dr. Hood explained that the smaller trials are helpful in that each consistently reached the same conclusion as DIG regarding the effect of digoxin on mortality—namely, that there is none.

In the DIG trial, however, there was a nonsignificant trend for fewer deaths from heart failure in digoxin-treated patients and a hint that the inotrope may have caused more arrhythmia deaths, although this wasn't a prespecified study end point.

Digoxin's effect on deterioration in clinical status was much more clear cut in the metaanalysis. The odds ratio for that end point was 0.31, meaning patients randomized to digoxin were 69% less likely to show significant clinical deterioration than were control patients. The third end point used in the metaanalysis was hospitalization for worsening heart failure. Patients on digoxin were 32% less likely to experience it.

Digoxin for heart failure is 'probably not first-line therapy. It's not very powerful.'

DR. HOOD

Two studies included in the metaanalysis were designed to learn whether concomitant ACE inhibitor therapy mattered in patients randomized to digoxin or placebo. Both showed that patients on an ACE inhibitor plus digoxin did better than those on an ACE inhibitor plus placebo.

However, the effects of digoxin in patients on other agents that have become first-line therapies in heart failure more recently than the ACE inhibitors, including β-blockers and aldosterone antagonists, haven't been systematically studied. For ethical reasons it's highly unlikely such trials will ever be done, Dr. Hood said. ■

β-Blocker Reverses Remodeling in Asymptomatic Heart Failure Patients

BOCA RATON, FLA. — A β-blocker can reverse cardiac remodeling and increase left ventricular ejection fraction in asymptomatic heart failure patients, according to a double-blind, randomized, placebo-controlled study presented at the annual meeting of the Heart Failure Society of America.

Metoprolol succinate extended-release tablets (Toprol-XL, AstraZeneca) are indicated for treatment of New York Heart Association class II and III patients with heart failure of ischemic, hypertensive, or cardiomyopathic origin. In symptomatic patients with heart failure and left ventricular systolic dysfunction, Toprol-XL reduced left ventricular volumes after 6 months of treatment in previous research, said Wilson S. Colucci, M.D.

To determine whether the once-daily agent provides a similar benefit in asymptomatic patients, Dr. Colucci and his colleagues randomized 164 NYHA class I patients at 44 U.S. sites to receive a 50-mg or 200-mg dose of metoprolol extended-release tablet daily or placebo.

All the participants in the Reversal of Ventricular Remodeling with Toprol-XL (REVERT) study had a baseline left ventricular ejection fraction (LVEF) below 40%. All also had evidence of cardiac remodeling at baseline, defined as a left ventricular end diastolic volume index greater than 75 mL/m^2. Mean age was 66 years, 25% were women, and 54% had heart failure of an ischemic etiology.

"In heart failure there are progressive enlargement and structural changes to the heart known as remodeling, which is initially compensatory but ultimately maladaptive," said Dr. Colucci, section chief of cardiovascular medicine at Boston University.

Left ventricular end systolic volume index was measured echocardiographically after 1 year. This index decreased by 15 mL/m^2 with the 200-mg dose of metoprolol, by 8 mL/m^2 with the 50-mg dose, and by 4 mL/m^2 with placebo. During the same year, LVEF increased 6% with the 200-mg dose, 4% with the 50-mg dose, and 0% with placebo.

"The REVERT study results show a reduction in this measure of left ventricular volume in asymptomatic heart failure patients with left ventricular systolic dysfunction," and they provide scientific data on cardiac remodeling in such patients, Dr. Colucci said.

The participants received metoprolol or placebo in addition to their existing medications. For example, at study entry, 92% were taking an ACE inhibitor or angiotension receptor blocker, and 65% were taking a diuretic. There were "very minimal changes" in medications during the study, and no participant used a cardiac resynchronization therapy device, he said.

"There was a very strong relationship between dose and heart rate decrease," he said. "We have not looked at whether anything in the demographics predicted that change."

Dr. Colucci has no conflict of interest disclosure regarding Toprol-XL. Its maker, AstraZeneca, sponsored the trial.

—Damian McNamara