Heart Failure Drug Combo Improves Survival 43%

In A-HeFT, Bidil was associated with a surprisingly large survival increase among African Americans.

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.

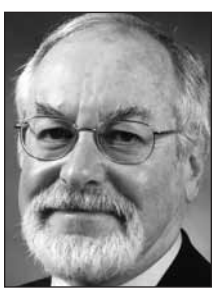
In the African American Heart Failure Trial (A-HeFT), the drug combination (BiDil, Nitromed Inc.) was associated with an increase in survival of 43% for African Americans with moderate to severe heart failure (N. Engl. J. Med. 2004;351:2049-57). The magnitude of this finding surprised some because the 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, Rasmussen Center for Cardiovascular Disease Prevention, University of Minnesota, Minneapolis. There was also a highly significant difference in LVIDd in the treatment group versus placebo group, he added.



'I would be surprised if the benefit ... 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." ■

β-Blocker Reverses Cardiac Remodeling in Heart Failure

BY DAMIAN McNAMARA
Miami Bureau

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.

When asked by an attendee about heart rate changes in the study, Dr. Colucci said, "There was a very strong relationship between dose and heart rate decrease. ... We have not looked at whether anything in the demographics predicted that change."

The REVERT study was sponsored by AstraZeneca. Dr. Colucci has no conflict of interest disclosure regarding the agent studied or AstraZeneca. ■

Left Ventricular Volume May Predict Cardiac Resynchronization Response

STOCKHOLM — A significant drop in left ventricular volume following implantation of a cardiac resynchronization device predicts the best clinical outcome in patients with severe heart failure, according to data from 141 patients.

"Left ventricular remodeling is an objective measure of efficacy" after cardiac resynchronization therapy (CRT), Cheuk-Man Yu, M.D., said at the annual congress of the European Society of Cardiology.

He reviewed the outcomes of patients with New York Heart Association class III or IV heart failure and dilated cardiomyopathy who received a CRT device at the Prince of Wales Hospital at the Chinese University in Hong Kong.

All patients had an echocardiogram at baseline and at 3-6 months after the CRT device was placed to assess the impact of CRT on cardiac size and function.

After an average follow-up of almost 2 years (695 days), 22 (15.6%) of the patients had died, mostly because of heart failure (9 patients) or cardiac arrest (6 patients). In addition, 19 patients were hospitalized for heart failure, and 21 patients were hospitalized for other cardiovascular disease.

An analysis of the echocardiographic changes that occurred between CRT implantation and the 3-6 month exam showed that patients who died during the first 1.9 years after treatment had significantly less early benefit from CRT, compared with patients who survived, reported Dr. Yu, chief of the division of cardiology at Prince of Wales Hospital.

For example, in patients who survived the follow-up period, left ventricular end-systolic volume fell by an average of 19.8% during the first few months of CRT, whereas in patients who died during follow-up, the average drop in end-systolic volume was 5.9%.

In a multivariate analysis, change in left ventricular end-systolic volume was the only significant predictor of long-term survival. Clinical parameters measured during the first few months after the start of CRT did not predict survival.

The reduction of end-systolic volume by less than 10% after CRT allowed for the prediction of all-cause death during the 1.9 years of follow-up, with a sensitivity of 70% and a specificity of 70%, said Dr. Yu. It also allowed for the prediction of death from a cardiovascular cause, with a sensitivity of 87% and a specificity of 69%.

Two factors seemed primarily responsible for limiting the reduction in left ventricular volume by CRT: suboptimal lead placement and a failure by CRT to reduce the QRS interval to less than 120 milliseconds, Dr. Yu said.

—Mitchel L. Zoler