

Clinical Trials

Isosorbide Dinitrate and Hydralazine in a Fixed-Dose Combination Produces Further Regression of Left Ventricular Remodeling in a Well-Treated Black Population With Heart Failure: Results From A-HeFT

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ABSTRACT

Background: Isosorbide dinitrate combined with hydralazine therapy compared with placebo in patients with heart failure resulted in a sustained increase in left ventricular (LV) ejection fraction (EF) indicative of regression of LV remodeling in the first Vasodilator-Heart Failure Trial (V-HeFT-I) in patients receiving only digoxin and diuretic. In the African-American Heart Failure Trial (A-HeFT) a fixed-dose combination resulted in a 43% reduction in mortality in 1050 black patients with heart failure already treated with recommended neurohormonal inhibiting drugs. Whether the fixed-dose combination produces a further regression of LV remodeling when added to renin-angiotensin and sympathetic inhibitors has not been documented.

Methods and Results: Echocardiograms at baseline and 6 months after randomization to placebo or a fixed-dose combination of isosorbide dinitrate/hydralazine (FDC I/H) were analyzed in 678 A-HeFT participants in a core laboratory. LVEF rose by 2.8 EF units in the FDC I/H group versus 0.8% in the control group ($P < .01$), LV mass index fell by 7.4 g/m² in the FDC I/H group versus an increase of 1.4 g/m² in the placebo group ($P < .05$), LV diastolic transverse diameter fell by 2.2 mm in FDC I/H and was unchanged in placebo ($P < .01$), and the LV systolic and diastolic sphericity indices improved in the FDC I/H group but remained unchanged in the placebo group. The mean plasma B-type natriuretic peptide (BNP) also measured in a core laboratory fell in the FDC I/H group by 39 pg/mL compared with 8 pg/mL in the placebo group ($P = .05$).

Conclusions: A fixed-dose combination of I/H produces regression of LV remodeling when added to background therapy with renin-angiotensin and sympathetic inhibitors in black patients with heart failure. This remodeling benefit may explain at least in part the mortality reduction in A-HeFT. (*J Cardiac Fail* 2007;13:331–339)

Key Words: Echocardiography, mortality, nitric oxide, heart failure, remodeling.

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Manuscript received November 6, 2006; revised manuscript received March 1, 2007; revised manuscript accepted March 5, 2007.

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All decisions regarding this manuscript were made by a guest editor.

A-HeFT was supported by NitroMed. The fixed-dose combination of isosorbide dinitrate and hydralazine was provided as BiDil.

All authors have received grant support from NitroMed, Inc (JNC, ISA, ALT), or are employees of NitroMed (MW, MLS, SWT). Dr. Cohn has a royalty relationship with NitroMed based on his patents of the drug combination.

1071-9164/\$ - see front matter

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doi:10.1016/j.cardfail.2007.03.001

Structural remodeling of the left ventricle, with a progressive increase in end-diastolic and end-systolic volume and decrease in ejection fraction, is characteristic of the natural history of heart failure.¹ The magnitude of remodeling has proved to be an important independent determinant of mortality and morbidity.^{2–5} Neurohormonal inhibiting drugs, such as angiotensin converting enzyme inhibitors (ACEI), β -blockers (BB), and angiotensin receptor blockers (ARB) have been demonstrated to inhibit the remodeling process. The structural effects of these therapies have been demonstrated to be linked to their favorable effect on survival.^{6–10}

In the first Vasodilator-Heart Failure Trial (V-HeFT-I) male patients with heart failure treated only with digoxin

and diuretic were randomly assigned to treatment with 2 vasodilator drugs, isosorbide dinitrate (ISDN) and hydralazine HCL (HYD), or their matching placebos. The vasodilator drug therapy resulted in a sustained increase in ejection fraction¹¹ that was quantitatively associated with improved survival.⁴ Because the survival benefit with ISDN/HYD was greater in the self-designated black patients than the white patients included in that study,¹² the African-American Heart Failure Trial (A-HeFT) was conducted to reaffirm the efficacy of a fixed-dose combination of ISDN and HYD (FDC I/H) in a black population receiving background therapy with neurohormonal inhibiting drugs.¹³ The 43% mortality reduction associated with FDC I/H in this trial¹⁴ was similar to the 47% reduction in the post-hoc analysis of the black population in V-HeFT.¹²

The purpose of this report is to provide an analysis of the echocardiographic data in A-HeFT to determine whether the mortality reduction in patients already well-treated with effective therapy could be attributed to a further regression of structural remodeling.

Methods

Details of the design and conduct of A-HeFT have previously been published.^{13,14} The study was carried out in self-designated African-American black patients with chronic heart failure who remained symptomatic while receiving treatment with standard recommended therapy for heart failure. Eligibility for the study was determined in part on the basis of screening echocardiograms performed and analyzed locally at individual study sites within 6 months of randomization. These screening echos were required to demonstrate an ejection fraction $\leq 35\%$ or, if $> 35\%$ but $< 45\%$, a transverse diameter of the left ventricle in diastole of ≥ 2.9 cm/m² body surface area or > 6.5 cm.

After eligibility was confirmed and the consent form signed, patients were stratified according to inclusion or noninclusion of a BB in their background therapy and were randomly assigned to treatment with a fixed-dose combination of ISDN 20 mg and HYD 37.5 mg or an identically appearing placebo. Drug therapy was initiated with 1 tablet 3 times daily and was uptitrated at 3 to 5 days, if tolerated, to a target of 2 tablets 3 times daily equivalent to 120 mg ISDN and 225 mg HYD daily.

Echocardiograms were performed at the time of randomization and 6 months after randomization. These echos were recorded on separate videotapes using a rigorous protocol and were sent for analysis to a core laboratory. All echo data were digitized by experienced echo technicians and analyzed by a single, experienced cardiologist who was blinded to treatment assignment, baseline, or 6-month study. Analyzed data included parasternal long and short axis; apical 2-, 3-, and 4-chamber views; and, when necessary, subcostal views. Doppler examination was not included. Ejection fraction (LVEF) was obtained from end-diastolic and end-systolic volumes calculated by the formula, $V = 0.85 A^2/L$, where V is volume of the LV cavity, A is area of the LV cavity, and L is maximum length of the LV cavity.¹⁵ Reported LVEF was the average of 3 separate determinations (5 in patients with atrial fibrillation). LV sphericity index (volume observed/volume of sphere using long axis as diameter) was calculated at end-systole and end-diastole using the formula, End-systolic or End-diastolic Volume in mL/[$(LAD^3 \times \pi)/6$], where LAD is the long axis in cm.^{16,17}

LV mass index (g/m²) was calculated by the formula, LV Mass (g) (M-mode) = $0.8\{1.04[(LVEDD + IVSd + PWd)^3 - LVEDD^3]\} + 0.6$, where LVEDD is the LV end-diastolic dimension (mm), PWd is the posterior wall thickness at end-diastole (mm), IVSd is the interventricular septal thickness at end-diastole (mm), and 1.04 is the specific gravity of the myocardium (g/m²). Data were indexed to body surface area (m²).^{18,19}

Blood samples were also collected at baseline and at the 6-month visit for analysis of B-type natriuretic peptide (BNP) levels. Plasma samples were frozen and stored at -70°C at ICON Laboratories (Farmingdale, New York) until analysis performed by Biosite, Inc (San Diego, California). The BNP assay procedure has been described in detail and validated previously.^{20,21}

Statistical Analyses

All LVEF, internal dimension at end-diastole (LVIDD), and BNP data were analyzed at baseline and after 6 months of follow-up. LVEF and LVIDD at baseline and 6 months, as well as their changes from baseline were compared between groups using the 2-sample *t*-test. For the analyses of death from any cause or first hospitalization for HF, standard Kaplan-Meier survival method with the log-rank test was used. Not all echo measurements were available in all patients at both time points. Only available data for any given measurement and time point are reported. The minimum detectable concentration for BNP is 5 pg/mL. Therefore, a value of 5 pg/mL was imposed for any recorded BNP values < 5 pg/mL. Because of the broad range and variability in BNP concentrations among subjects, for comparison of BNP between treatment groups, both arithmetic means $\pm$ SD and geometric means with 95% confidence interval and *P* values for the geometric mean using the 2-sample *t*-test are presented.

Results

A total of 1050 patients were entered into the A-HeFT study, 518 randomized to FDC I/H and 532 to placebo. Not all centers collected echo data after randomization and some of the echos were excluded from analysis because of inadequacy of the images. Furthermore, the study was terminated prematurely by the Data Safety Monitoring Board because of excess mortality in the placebo group. Therefore, many of the randomized patients did not reach the 18-month follow-up target and the study was terminated before all randomized patients reached the 6-month time point for follow-up echo assessment. Paired analysis of baseline and 6-month ejection fractions were available in 666 patients (328 randomized to FDC I/H, 338 to placebo). Baseline and 6-month LVIDDs were available in 678 patients (337 FDC I/H and 341 placebo).

The baseline characteristics of the 678 patients whose echo data were used are displayed in Table 1. These characteristics are essentially identical to those of the entire A-HeFT population previously reported.¹⁴ The reported prestudy EF and LVIDD which determined eligibility were collected up to 6 months before randomization and were analyzed locally. Concomitant medication use at baseline and at 6 months after randomization is shown in Table 2. Most patients were treated with diuretics, renin-angiotensin system inhibitors and BB. Background therapy

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