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Isosorbide Dinitrate Plus Hydralazine in Blacks with Heart Failure

Lead author: Joseph A. Woelfel, Ph.D. FASCP, R.Ph., Assistant Editor

Background
Heart failure (HF) is a major public health problem and is more common in the black population. It affects approximately 3% of all adult black Americans. Black patients develop HF symptoms at an earlier age than non-black patients. This may be due to the fact that black patients are more likely to have hypertension and diabetes than non-black patients. They more frequently exhibit sodium retention, ventricular hypertrophy, and vascular injury. When diagnosed, HF progresses more rapidly in black than in white patients, as evidenced by a higher risk of initial and recurrent hospitalization and death.¹

In the U. S. the prevalence of high blood pressure (HBP) in African Americans is among the highest in the world. They develop HBP earlier in life and have higher average blood pressures. Blacks have a 1.3 times greater rate of nonfatal stroke, a 1.8 times greater rate of fatal stroke, a 1.5 times greater rate of heart disease death, and a 4.2 times greater rate of end-stage renal disease than whites.²

Because racial minorities with HF are underrepresented in HF clinical trials of new drugs, little is known about their response to medications used in the management of HF. Recommendations for management of HF call for control of systolic and diastolic hypertension.¹

Most African Americans require combination antihypertensive therapy to reach appropriate blood pressure levels. The Hypertension in African Americans Working (HAAW) Group’s consensus statement suggests the combination of agents to achieve target blood pressure when required. Combinations include beta-blocker/diuretic, angiotensin-converting enzyme inhibitor (ACEI)/diuretic, ACEI/calcium-channel blocker (CCB), or angiotensin-receptor blocker (ARB)/diuretic dual therapies.³

The African-American Heart Failure Trial (A-HeFT) suggests possible new combinations using older drugs.⁴

Citation

Methods
This study was a randomized, placebo-controlled, double-blind trial of 1,050 black patients at least 18 years of age or older. These self-identified African Americans had New York Heart Association class III or IV heart failure with dilated ventricles. All had a baseline mean ejection fraction of 24% and were already receiving standard therapy for heart failure. Patients were randomly assigned to receive fixed doses of isosorbide dinitrate (20 to 40 mg) plus hydralazine (37.5 to 75 mg) orally three times daily or placebo three times daily. In addition all participants continued their standard heart failure therapy. Standard therapy included diuretics, ACEIs, ARBs, beta-blockers, carvedilol, digoxin, or spironolactone. Stratification into groups was based on use or nonuse of beta-blockers.

The study primary end point was a composite score of weighted values combining death from any cause, a first hospitalization for heart failure, and change in the quality of life. Individual scores could range from +2 (positive outcome) to -6 (negative outcome). Patients were followed for 18 months.

Results
There were 518 patients that received isosorbide dinitrate combined with hydralazine compared with 532 placebo recipients. The primary composite score was -0.1 ± 1.9 in the
treatment group compared with -0.5 ±2.0 in the placebo group (P=0.01). Individual endpoints were 43% reduction in the rate of death from any cause (hazard ratio, 0.57, P = 0.01), 33% relative reduction in the rate of first hospitalization for heart failure (16.4% vs. 22.4%, P= 0.001), and improvement in the quality of life (change in score, -5.6 ±20.6 vs. -2.7 ±21.2, with lower scores indicating better quality of life, P= 0.02, range of possible values, 0 to 105).

The trial was stopped after a ten month mean duration of follow-up when survival analysis revealed a significantly higher mortality rate in the placebo group than in the treatment group (10.2% vs. 6.2%, P=0.02).

**Author Conclusions**

Isosorbide dinitrate plus hydralazine in a fixed dosage combined with existing standard heart failure therapy was beneficial and increased survival in black heart failure patients.

**Commentary**

The mortality benefit of combined isosorbide dinitrate with hydralazine was described in an earlier study of Veterans Administration male patients already receiving digoxin and diuretics (Vasodilator-Heart Failure Trial (V-HeFT I). This randomized, placebo-controlled, double-blind study identified a 36% mortality-risk reduction by three years in the trial group treated with isosorbide plus hydralazine (I-H), compared with a prazosin-treatment group, and a placebo-treatment group. The majority of patients in this trial were non-African American; however the greatest benefit was shown in the African American I-H-treated group.5

Studies of vasodilatory drug effects in African Americans have shown a reduced response to nitric oxide-mediated therapies.6,7 Isosorbide dinitrate stimulates the nitric oxide pathway and hydralazine has antioxidant properties that inhibit superoxide synthesis. The combined effects of these two agents may help restore the balance of nitric oxide and superoxide synthesis in African Americans by dilating both arteries and veins.8

Other antihypertensive agents have been identified as less effective in blacks. Beta-blockers and ACEIs, when administered as monotherapy, were less effective in blood pressure-lowering efficacy for black as compared with white patients.3 Enalapril (Vasotec) is an example of an ACEI found to have less antihypertensive effect in black patients than in non-blacks.9 In addition, it should be noted that black patients receiving ACEIs have been reported to have a higher incidence of angioedema compared to non-blacks. The African-American Study of Kidney Disease and Hypertension Study Group identified the CCB, amlodipine (Norvase), as less renoprotective compared with the ACEI, ramipril (Altace), in blacks with hypertensive renal insufficiency.10 The antihypertensive effect of the ARB, losartan (Cozaar), is somewhat less in black patients.11

Despite these differences, all antihypertensive drug classes are associated with blood pressure lowering efficacy and improved outcomes in blacks as well as non-blacks.3

A new drug application has been filed with the FDA by NitroMed Inc. for a combination product containing isosorbide dinitrate and hydralazine. The product BiDil will be a fixed-dose oral combination. It will be indicated for the treatment of heart failure in African Americans. Product launch is expected in 2005.12

As demonstrated in this study by Taylor et al the addition of isosorbide dinitrate plus hydralazine as a fixed-dose combination with standard heart failure therapy is efficacious and increases survival in black patients [Evidence level A; high-quality RCT].4

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

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References


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