

Isosorbide dinitrate plus hydralazine was effective for advanced heart failure in black patients

Taylor AL, Ziesche S, Yancy C, et al. **Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.** *N Engl J Med.* 2004;351:2049-57.

QUESTION

In black patients with New York Heart Association (NYHA) class III or IV heart failure (HF) with dilated ventricles, is a fixed dose of isosorbide dinitrate plus hydralazine (ID + H) better than placebo?

METHODS

Design: Randomized placebo-controlled trial (African-American Heart Failure Trial [A-HeFT]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, data collectors, outcome assessors, monitoring committee, and statisticians).*

Follow-up period: 18 months.

Setting: 161 centers in the United States.

Patients: 1050 patients \geq 18 years of age (mean age 57 y, 60% men) self-identified as black (defined as African descent) who had NYHA class III or IV HF for \geq 3 months, had left ventricular dysfunction in the preceding 6 months, and were receiving standard therapy for HF. Exclusion criteria included acute myocardial infarction, stroke, cardiac surgery, or percutaneous coronary intervention within the preceding 3 months; clinically significant valvular heart disease; hypertrophic or restrictive cardiomyopathy; active myocarditis; and uncontrolled hypertension.

Intervention: Patients were stratified for use and nonuse of β -blockers and allocated to

isosorbide dinitrate, 20 mg, plus hydralazine hydrochloride, 37.5 mg, in 1 tablet 3 times daily ($n = 518$), or placebo ($n = 532$). The dose was increased to 2 tablets 3 times daily in the absence of side effects.

Outcomes: Composite score of weighted values for all-cause death, first hospitalization for HF during 18-month follow-up, and change in quality of life at 6 months (possible score -6 to $+2$ [higher scores = better outcome]). Secondary outcomes included individual components of the composite endpoint.

Patient follow-up: 100% (intention-to-treat analysis).

MAIN RESULTS

Based on a prespecified interim analysis, the study was stopped after 1050 of the planned 1100 patients were randomized because of

higher mortality rate in the placebo group. At study termination, the composite endpoint score was more improved in patients receiving ID + H than in those receiving placebo (Table). The individual components of the composite endpoint were also improved with ID + H (Table).

CONCLUSION

In black patients with New York Heart Association class III or IV heart failure with dilated ventricles, fixed-dose isosorbide dinitrate plus hydralazine improved survival and quality of life better than placebo.

Source of funding: NitroMed.

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*See Glossary.

Isosorbide dinitrate plus hydralazine (ID + H) vs placebo for heart failure (HF) in black patients at mean 10 months†

Outcomes	ID+H	Placebo	95% CI for the difference	
Mean composite score‡	-0.1	-0.5	0.16 to 0.64	
Change in mean QOL score at 6 mo	-5.6	-2.7	0.37 to 5.4	
			RRR (CI)	NNT (CI)
All-cause death	6.2%	10%	39% (7.7 to 60)	26 (14 to 150)
First hospitalization for HF	16%	24%	33% (14 to 47)	13 (8 to 32)

†QOL = quality of life. Lower scores indicate better quality of life. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

‡Composite score (weighted values for all-cause death, first hospitalization for HF during 18-mo follow-up, and change in quality of life at 6 mo) ranged from -6 to $+2$, with higher scores indicating better outcome.

COMMENTARY

The A-HeFT trial convincingly shows that ID + H reduces mortality, morbidity, and symptoms in self-identified African-Americans with low ejection fraction HF. Why was the trial restricted to black patients? The investigators rationalize this approach based on post hoc analyses of the V-HeFT I and II trials (1), which showed significant differences between black and white HF patients (blacks were less likely to have underlying coronary artery disease and more likely to have nonischemic cardiomyopathy) and substantial evidence of efficacy with ID + H only in blacks. It has also been speculated that this population was selected because it might facilitate more rapid approval, more successful marketing, and longer patent protection. Whether these points are true is arguable, but previous data (1) indicate that this was a reasonable hypothesis to test, despite the politically and scientifically charged atmosphere surrounding race-based therapeutics.

What is the mechanism of benefit with ID + H? Limited data show that it may prolong the activity of nitric oxide and prevent the generation of reactive oxygen species. Alternative explanations include the known hemodynamic effects of this combination and the potential to reverse left ventricular dilatation and to mitigate secondary mitral

regurgitation, which is more prevalent in nonischemic cardiomyopathy.

How should clinicians use ID + H in light of the A-HeFT results? The race-based design and lack of efficacy data in whites leave no alternative to making race-based recommendations. ID + H should become standard care in black patients with systolic HF who fulfill the A-HeFT entry criteria and arguably in patients with milder symptoms. For whites, ID + H might be used empirically, but primarily only in patients who continue to have evidence of progression despite regimens that include β -blockers, angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers if intolerant), and aldosterone blockers, plus diuretics and possibly digoxin. With this degree of polypharmacy, physicians and patients may be reluctant to use another treatment of unproven value in nonblacks.

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Reference

1. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail.* 1999;5:178-87.