

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.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Internal medicine ★★★★★☆ Cardiology ★★★★★☆

Q 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: randomised 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 centres in the US.

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

Intervention: patients were stratified for use and non-use 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 hospital admission for HF during 18 month follow up, and change in quality of life at 6 months.

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

*See glossary.

MAIN RESULTS

Based on a prespecified interim analysis, the study was stopped after 1050 of the planned 1100 patients were randomised because the placebo group had more deaths. The table shows the results.

CONCLUSION

In black patients with advanced heart failure, fixed dose isosorbide dinitrate plus hydralazine improved survival and quality of life.

Abstract and commentary also appear in ACP Journal Club

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 but raises several questions. Why was the trial restricted to black patients? The investigators rationalise 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 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 and longer patent protection. Whether these points are true is arguable, but previous data¹ 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 haemodynamic effects of this combination and the potential to reverse left ventricular dilatation and to mitigate secondary mitral regurgitation, which is more prevalent in non-ischaemic 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 leaves 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 symptoms or 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 and limited data in whites, physicians and patients may be reluctant to add a thrice-daily drug.

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1 Carson P, Ziesche S, Johnson G, *et al.* *J Card Fail* 1999;**5**:178-87.

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Isosorbide dinitrate plus hydralazine (ID+H) v 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	
Mean QOL score change 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 hospital admission for HF	16%	24%	33% (14 to 47)	13 (8 to 32)

*QOL = quality of life. Lower scores indicate better quality of life. †Composite score (weighted values for all cause death, first hospital admission 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.