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


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

Methods

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?

**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, 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 data 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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### Table: Isosorbide dinitrate plus hydralazine (ID+H) vs placebo for heart failure (HF) in black patients at mean 10 months*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ID+H</th>
<th>Placebo</th>
<th>95% CI for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean composite score†</td>
<td>−0.1</td>
<td>−0.5</td>
<td>0.16 to 0.64</td>
</tr>
<tr>
<td>Mean QOL score change at 6 mo</td>
<td>−5.6</td>
<td>−2.7</td>
<td>0.37 to 3.4</td>
</tr>
<tr>
<td>All cause death</td>
<td>6.2%</td>
<td>10%</td>
<td>39% (7.7 to 60)</td>
</tr>
<tr>
<td>First hospital admission for HF</td>
<td>16%</td>
<td>24%</td>
<td>33% (14 to 47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26 (14 to 150)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13 (8 to 32)</td>
</tr>
</tbody>
</table>

*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 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.
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*Evid Based Med* 2005 10: 44
doi: 10.1136/ebm.10.2.44

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