Treatment with Hydralazine and Nitrates

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Hydralazine and Isosorbide Dinitrate in Heart Failure

- Historical perspective.
- Mechanisms.
- When and How to use it.
- Why use hydralazine?
- Should it be Use in Non African Americans?
Hemodynamic Advantage of Combined Hydralazine and Nitrates

Am J Cardiol 1977
To a point, increasing preload will increase stroke volume of the heart (balloon). After that point is reached, further increases in preload do not improve stroke volume much.

**Frank-Starling curves in CHF** Idealized family of Frank-Starling curves produced by worsening ventricular function in heart failure. In ventricles with normal cardiac performance, there is a steep and positive relationship between increased cardiac filling pressures (as estimated from the left ventricular end-diastolic or pulmonary capillary wedge pressure) and increased stroke volume or cardiac output (top curve). In comparison, during progression from mild to severe myocardial dysfunction, this relationship is right-shifted (ie, a higher filling pressure is required to achieve the same cardiac output) and flattened so that continued increases in left heart filling pressures lead to minimal increases in cardiac output at the possible expense of pulmonary edema. The onset of mild heart failure results in an initial reduction in cardiac function (point B), a change that can be normalized, at least at rest, by raising the LVEDP via fluid retention (point C). In comparison, normalization of stroke volume is not attainable in severe heart failure (bottom curve).
EFFECT OF VASODILATOR THERAPY ON MORTALITY IN CHRONIC CONGESTIVE HEART FAILURE

Results of a Veterans Administration Cooperative Study*


Abstract To evaluate the effects of vasodilator therapy on mortality among patients with chronic congestive heart failure, we randomly assigned 642 men with impaired cardiac function and reduced exercise tolerance who were taking digoxin and a diuretic to receive additional double-blind treatment with placebo, prazosin (20 mg per day), or the combination of hydralazine (300 mg per day) and isosorbide dinitrate (160 mg per day). Follow-up averaged 2.3 years (range, 6 months to 5.7 years). Mortality over the entire follow-up period was lower in the group that received hydralazine and isosorbide dinitrate than in the placebo group. This difference was of borderline statistical significance. For mortality by two years, a major end point specified in the protocol, the risk reduction among patients treated with both hydralazine and isosorbide dinitrate was 34 percent (P<0.028). The cumulative mortality rates at two years were 25.6 percent in the hydralazine–isosorbide dinitrate group and 34.3 percent in the placebo group; at three years, the mortality rate was 36.2 percent versus 46.9 percent. The mortality-risk reduction in the group treated with hydralazine and isosorbide dinitrate was 36 percent by three years. The mortality in the prazosin group was similar to that in the placebo group. Left ventricular ejection fraction (measured sequentially) rose significantly at eight weeks and at one year in the group treated with hydralazine and isosorbide dinitrate but not in the placebo or prazosin groups.

Our data suggest that the addition of hydralazine and isosorbide dinitrate to the therapeutic regimen of digoxin and diuretics in patients with chronic congestive heart failure can have a favorable effect on left ventricular function and mortality. (N Engl J Med 1986; 314:1547-52.)
The V-HeFT I Trial

642 men with chronic heart failure. Mean EF of 30%, mean max VO2 14.5 ml/Kg/min, on digoxin and diuretics. Randomized to either placebo (N=273), prazosin (20 mg/d, N=183) or Hydralazine/ISDN (300/160 mg/d N=186). Average doses: Hydralazine 270 mg/d, ISDN 136 mg/d.
V-HeFT I Study
Effect on all cause mortality

34% mortality reduction for 1st 2 y with Hyd-Iso
P=0.028

Figure 1. Cumulative Mortality from the Time of Randomization in the Three Treatment Groups.
V-HeFT I Study
Effect on all cause mortality

Table 3. Cumulative Mortality Rates at Each Anniversary of Randomization in the Placebo and Hydralazine–Isosorbide Dinitrate (Hyd–Iso) Groups.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. Alive at Start</th>
<th>Cumulative Mortality</th>
<th>Mortality Reduction in Hyd–Iso Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLACEBO HYD–ISO</td>
<td>PLACEBO HYD–ISO</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>273 186</td>
<td>19.5 12.1</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>201 147</td>
<td>34.3 25.6</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>134 108</td>
<td>46.9 36.2</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>82 70</td>
<td>53.6 49.7</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>40 36</td>
<td>——</td>
<td>——</td>
</tr>
</tbody>
</table>

*Based on life-table point estimate of mortality rates at the anniversary. Mortality-risk reductions that yielded an estimate of overall difference between survival curves up to the anniversary were 34 percent at two years and 36 percent at three years.
EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

253 class IV HF patients randomized to placebo or enalapril

Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.
A COMPARISON OF ENALAPRIL WITH HYDRAZONE–ISOSORBIDE DINITRATE IN THE TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE

JAY N. COHN, M.D., GARY JOHNSON, M.S., SUSAN ZIESCHE, R.N., FREDERICK COBB, M.D., GARY FRANCIS, M.D., FELIX TRISTANI, M.D., RAPHAEL SMITH, M.D., W. BRUCE DUNKMAN, M.D., HENRY LOEB, M.D., MAYLENE WONG, M.D., GEEVHA BHAT, M.D., STEVEN GOLDMAN, M.D., ROSS D. FLETCHER, M.D., JAMES DOHERTY, M.D., C. VINCENT HUGHES, M.D., PETER CARSON, M.D., GUILLERMO CINTRON, M.D., RALPH SHABETAI, M.D., AND CLAIR HAUKENSON, M.S.*

Abstract Background and Methods. To define better the efficacy of vasodilator therapy in the treatment of chronic congestive heart failure, we compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for heart failure. The patients were randomly assigned in a double-blind manner to receive 20 mg of enalapril daily or 300 mg of hydralazine plus 160 mg of isosorbide dinitrate daily. The latter regimen was identical to that used with a similar patient population in the effective-treatment arm of our previous Vasodilator–Heart Failure Trial.

Results. Mortality after two years was significantly lower in the enalapril arm (18 percent) than in the hydralazine–isosorbide dinitrate arm (25 percent) (P = 0.016; reduction in mortality, 28.0 percent), and overall mortality tended to be lower (P = 0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (New York Heart Association class I or II). In contrast, body oxygen consumption at peak exercise was increased only by hydralazine–isosorbide dinitrate treatment (P<0.05), and left ventricular ejection fraction, which increased with both regimens during the 2 years after randomization, increased more (P<0.05) during the first 13 weeks in the hydralazine–isosorbide dinitrate group.

Conclusions. The similar two-year mortality in the hydralazine–isosorbide dinitrate arms in our previous Vasodilator–Heart Failure Trial (26 percent) and in the present trial (25 percent), as compared with that in the placebo arm in the previous trial (34 percent), and the further survival benefit with enalapril in the present trial (18 percent) strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine–isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination. (N Engl J Med 1991; 325:303-10.)
The V-HeFT II Trial

804 men receiving digoxin and diuretics for HF. Randomly assigned to receive 20 mg of enalapril daily or 300 mg of hydralazine plus 160 mg of ISDN daily.

lower in the enalapril arm (18 percent) than in the hydralazine–isosorbide dinitrate arm (25 percent) (P = 0.016; reduction in mortality, 28.0 percent), and overall mortality tended to be lower (P = 0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (New York Heart Association class I or II). In con-
Change in EF and maximum oxygen consumption higher with nitrates

**Figure 2.** Mean Change from Base Line in Left Ventricular Ejection Fraction over the First Two Years of the Study in Each Treatment Arm.

**Figure 3.** Mean Change from Base Line in Peak Oxygen Consumption over the First Two Years of the Study in Each Treatment Arm.

Ejection Fraction  
\( P < 0.05 \)

Oxygen Consumption  
\( P < 0.01 \)
Effect of Enalapril vs. HYD/ISDN on all cause mortality

P = 0.016 at 2 years and 0.08 overall
Mortality difference due to decreased sudden death

Mortality reduction
More prominent in class I-II patients
V–HeFT Studies
Racial Differences in Response to Therapy
Annual Mortality Rate

V – HeFT I 180 AA vs. 450 white male patients.  P = 0.04

V – HeFT II 215 AA vs. 574 white patients.  P = 0.02

Carson P et al J Cardiac Fail 1999;5:178
Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D’Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*

ABSTRACT

BACKGROUND
We examined whether a fixed dose of both isosorbide dinitrate and hydralazine provides additional benefit in blacks with advanced heart failure, a subgroup previously noted to have a favorable response to this therapy.

METHODS
A total of 1050 black patients who had New York Heart Association class III or IV heart failure with dilated ventricles were randomly assigned to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for heart failure. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and change in the quality of life.

RESULTS
The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine (10.2 percent vs. 6.2 percent, P=0.02). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group (−0.1±1.9 vs. −0.5±2.0, P=0.01; range of possible values, −6 to +2), as were its individual components (43 percent reduction in the rate of death from any cause [hazard ratio, 0.57; 95 percent confidence interval, 0.38 to 0.85]; hazard ratio, 0.57; 95 percent confidence interval, 0.38 to 0.85). The results were similar in both men and women, although more women than men were included in the study.

*Participants in the African-American Heart Failure Trial (A-HeFT) are listed in the Appendix.
1050 AA patients with HFrEF. NYHA functional class III-IV. Randomly assigned to a fixed dose of ISDN plus hydralazine (Bidil) or placebo in addition to standard HF therapy. Primary end point: A composite of death, hospitalizations and QOL.
A-HeFT Results: Additional 39% Risk Reduction in First Hospitalization for Heart Failure When Added to Current Standard Therapies
## A-HeFT Hospitalizations

<table>
<thead>
<tr>
<th>Heart Failure–Related</th>
<th>Standard Therapies + BiDil (n=518)</th>
<th>Standard Therapies + Placebo (n=532)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># of hospitalizations</td>
<td>173</td>
<td>251</td>
<td></td>
</tr>
<tr>
<td>Mean # of hospitalizations per patient</td>
<td>0.33</td>
<td>0.47</td>
<td>0.002</td>
</tr>
<tr>
<td>Total # of days in the hospital – all patients</td>
<td>1167</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Mean # of days in the hospital per patient</td>
<td>2.3</td>
<td>3.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean # of days per hospitalization</td>
<td>6.7</td>
<td>7.9</td>
<td>0.006</td>
</tr>
</tbody>
</table>
A-HeFT
Quality of Life

Change in MLHF® Questionnaire Score

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Standard Therapies + BiDil</th>
<th>Standard Therapies + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-9.2</td>
<td>-8.8</td>
</tr>
<tr>
<td>6</td>
<td>-8.5</td>
<td>-7.8</td>
</tr>
<tr>
<td>9</td>
<td>-8.2</td>
<td>-7.5</td>
</tr>
<tr>
<td>12</td>
<td>-7.9</td>
<td>-7.1</td>
</tr>
<tr>
<td>15</td>
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<td>-6.9</td>
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<tr>
<td>18</td>
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<td>-6.6</td>
</tr>
<tr>
<td>End point</td>
<td>-7.0</td>
<td>-6.3</td>
</tr>
</tbody>
</table>

*P<0.05  †P<0.01

BiDil, n = 423
Placebo, n = 441

MLHF® Questionnaire=Minnesota Living With Heart Failure® Questionnaire.
A-HeFT
Effect on Mortality

A-HeFT Results: Additional 43% Reduction in Mortality When Added to Current Standard Therapies

- Standard Therapies + BiDil
  - Event rate = 6.2%
  - $P = 0.012$ by Log-Rank Test
- Standard Therapies + Placebo
  - Event rate = 10.2%

BiDil, n = 518
463 407 360 314 253 16
Effect on Mortality of Various HF Medications

## Table 18. Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>
HYD+ISDN or ICD?

12% reduction in death and hospitalization
P=0.002

4.5 mg/d Vs 33 mg/d
43% improvement in survival in 10 months
P=0.01

23% survival benefit with ICD in 45 months
P<0.001

SCD - HeFT

A - HeFT
Hydralazine and Oral Nitrates
When To Use It?

A combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in addition to BB and ACE-inhibitors for African Americans with HF and reduced LVEF:

- NYHA III or IV HF
  Strength of Evidence = A
- NYHA II HF  Strength of Evidence = B

AHA/ACC 2013 Practice Guideline
Despite proven benefits, the combination hydralazine and nitrate therapy is not commonly used in HF.
Heart Failure Readmission Penalties, Care Quality, and Outcomes
Pandey et al. JACC Heart Failure August 2016

**Figure 1** Adherence to Get With The Guidelines-Heart Failure Performance Measures Across the Study Groups

- N=43,143
- GWTG-HF Registry
- 2008-2011
In practice, patients receive lower doses than those proved beneficial in clinical trial.

It is unknown whether lower doses provide either meaningful vasodilation, protection against tolerance or clinical benefit.
## Daily Dose for Bidil

<table>
<thead>
<tr>
<th></th>
<th>1st Dose</th>
<th>2nd Dose</th>
<th>3rd Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Dose† ‡</td>
<td><img src="image1" alt="Dosage" /></td>
<td><img src="image2" alt="Dosage" /></td>
<td><img src="image3" alt="Dosage" /></td>
</tr>
<tr>
<td><strong>Starting Dose‡ ‡</strong></td>
<td><img src="image4" alt="Dosage" /></td>
<td><img src="image5" alt="Dosage" /></td>
<td><img src="image6" alt="Dosage" /></td>
</tr>
<tr>
<td>37.5 mg / 20mg</td>
<td><img src="image7" alt="Dosage" /></td>
<td><img src="image8" alt="Dosage" /></td>
<td><img src="image9" alt="Dosage" /></td>
</tr>
<tr>
<td><strong>Maximum Dose††</strong> (if tolerated)</td>
<td><img src="image10" alt="Dosage" /></td>
<td><img src="image11" alt="Dosage" /></td>
<td><img src="image12" alt="Dosage" /></td>
</tr>
<tr>
<td>75 mg / 40 mg</td>
<td><img src="image13" alt="Dosage" /></td>
<td><img src="image14" alt="Dosage" /></td>
<td><img src="image15" alt="Dosage" /></td>
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</tbody>
</table>
## Hydralazine / ISDN

### What is the Dose?

#### Daily Dose for Bidil

<table>
<thead>
<tr>
<th></th>
<th>1st Dose</th>
<th>2nd Dose</th>
<th>3rd Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Dose† ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting Dose‡ ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Dose¶ ¶¶ (if tolerated)</td>
<td><strong>Mean dose in A-HeFT:</strong> &lt;br&gt;Hydralazine 142 mg/d &lt;br&gt;ISDN 76 mg/d</td>
<td><strong>Mean dose in A-HeFT:</strong> &lt;br&gt;Hydralazine 142 mg/d &lt;br&gt;ISDN 76 mg/d</td>
<td><strong>Mean dose in A-HeFT:</strong> &lt;br&gt;Hydralazine 142 mg/d &lt;br&gt;ISDN 76 mg/d</td>
</tr>
</tbody>
</table>
Why Use Hydralazine?

- **Isosorbide dinitrate** releases nitric oxide, dilates arteries and veins.
- **Hydralazine HCl** may also mitigate tolerance to nitrates, dilates arteries.
ISDN in HF
Elkayam U et al, circulation 1991;84:2040
1. Increased endothelial and VSM mitochondrial superoxide formation.
2. Direct inhibition of NOS activation.
3. Uncoupling of NOS caused by peroxynitrite
4. Vasoconstrictor super sensitivity
   Due to activation of protein kinase C (PKG)
5. ↓ bioactivation of GTN.

NADPH - Nicotinamide Adenine Dinucleotide Phosphate.  ALDH-2-Aldehyde Dehydrogenase.  PKC - Protein Kinase C.  GTP-CH( cyclohydrolase), A cofactor of NO Synthase.  B4 - tetrahydrobiopterin, A cofactor of NOS,  ONOO - : Peroxynitrite  

saga = Soluble Guanylyl Cyclase
Consequences of Nitric Oxide and Super Oxide Balance Disruption in Heart Failure Patients

Potential Mechanisms of Hydralazine – Induced Prevention of Nitrate Tolerance

- Marked reduction of vascular superoxide levels by inhibition of NADH oxidase (Munzel, JCI 1996).
- Direct free radical scavenger due to alteration in vascular inducible NOS/COX-2 gene expression (Leiro, Int Immunopharmacol 2004).
- Inhibition of peroxynitrite formation (Daiber, BBRC 2005)
Oxidative Stress Concept of Nitrate Tolerance and the Antioxidant Properties of Hydralazine

(Munzel et al., J Clin Invest 1996;98:1465-1470)

Figure 2. Effects of in vivo hydralazine treatment on vascular superoxide production (A) and vascular nitroglycerin (NTG) sensitivity (B) in control and NTG-treated animals. Treatment with hydralazine significantly reduced superoxide production in vessels from control and NTG-treated animals and simultaneously prevented the development of tolerance. Values are expressed as mean ± SEM of 4 to 12 experiments. *p = 0.01 untreated versus NTG-treated; †p = 0.05 versus without hydralazine treatment. (Adapted with permission from J Clin Invest.)
Prevention of tolerance to NTG with Hydralazine

Bauer JA Circulation 1991;84:35

- Hemodynamic effects in rats with HF
- Hydralazine prevents tolerance to NTG in rat HF model

Prevention of Nitrate Tolerance with Hydralazine in Patients with Heart Failure

Gogia H, Elkayam U. JACC 1995;26:575

* $P<0.05$ vs 0 hours.
Why Use Hydralazine?

- Isosorbide dinitrate
  - Releases nitric oxide
  - Dilates arteries and veins

- Hydralazine HCl
  - May also mitigate tolerance to nitrates
  - Dilates arteries
Change in BP during therapy

Figure 3
Time Course of Mean SBP and DBP Change in the Placebo and FDC I/H Groups
Change in BP in relation to baseline BP

Anand et al JACC 207;49:32-9
Effect of baseline BP on morbidity and mortality


Figure 2

Effect of FDC I/H Treatment on Mortality and Morbidity by Median Baseline SBP

Median SBP = 126 mmHg
## Adverse Effects

### Table 4. Adverse Events.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Isosorbide Dinitrate plus Hydralazine</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations of CHF</td>
<td>8.7%</td>
<td>12.8%</td>
<td>0.04</td>
</tr>
<tr>
<td>Severe exacerbation of CHF</td>
<td>3.1%</td>
<td>7.0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Headache</td>
<td>47.5%</td>
<td>19.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>29.3%</td>
<td>12.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Should Hyd/Nitrare therapy be used in non AA patients?
A combination of hydralazine and ISDN can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. *(Level of Evidence: B)*
Change in EF and maximum oxygen consumption higher with nitrates

Figure 2. Mean Change from Base Line in Left Ventricular Ejection Fraction over the First Two Years of the Study in Each Treatment Arm.

Ejection Fraction
P < 0.05

Figure 3. Mean Change from Base Line in Peak Oxygen Consumption over the First Two Years of the Study in Each Treatment Arm.

Oxygen Consumption
P < 0.01

different effects of the two regimens (enalapril and hydralazine–isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination. (N Engl J Med 1991; 325:303-10.)
Hyd/ISDN in Patients D/C from Hospital
Mullens W et al. Am J Cardiol 2009;103;1113

80% Caucasians
SBP 108 ± 16 mmHg
Mean PWP 24 ± 8 mmHg

Freedom from all cause mortality

Freedom from mortality and hospitalizations
Nitrates in patients with HFrEF in the CHAMPION study

- Increased furosemide dose by 51 mg/d
- Increased nitrates dose by 18 mg/d
Hemodynamic Effects of Hydralazine/Nitrate Combination

Roth, Elkayam AHJ 1993;125:155
Table 1. Baseline Characteristics of 27 Responders and 23 Nonresponders to 40 mg of Isosorbide Dinitrate

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 27)</th>
<th>Nonresponders (n = 23)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Symptom duration (mo)</td>
<td>37 ± 40</td>
<td>22 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (n = 45)</td>
<td>0.23 ± 0.07</td>
<td>0.24 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>10 ± 6</td>
<td>14 ± 5</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>PAW</td>
<td>27 ± 7</td>
<td>30 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>PA</td>
<td>40 ± 8</td>
<td>41 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>2.1 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>24 ± 7</td>
<td>21 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>91 ± 16</td>
<td>94 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95 ± 14</td>
<td>92 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (dynes-s-cm⁻⁵)</td>
<td>1827 ± 491</td>
<td>1718 ± 407</td>
<td>NS</td>
</tr>
<tr>
<td>PVR (dynes-s-cm⁻⁵)</td>
<td>398 ± 557</td>
<td>260 ± 146</td>
<td>NS</td>
</tr>
<tr>
<td>SWI (g.m/m²)</td>
<td>23 ± 11</td>
<td>18 ± 9</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI = cardiac index; HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PA = pulmonary arterial pressure; PAW = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.

Figure 3. Response to high dose (80 to 120 mg) isosorbide dinitrate (ISDN) in 23 nonresponders to the 40 mg dose. D/C = excluded from study.
Hyd/ISDN combination (Bidil) is one of the most effective and underutilized interventions for the treatment of AA patients with symptomatic HFrEF.

Hyd/ISDN is recommended to patients not tolerating angiotensin blocking therapy regardless of race.
Summary

- Hydralazine improves hemodynamic effect and prevents attenuation of nitrates effect due to tolerance.
- Hyd/ISDN should be considered in non AA patients with severe HF for improvement of hemodynamics and possible outcome.
Summary

- When used for hemodynamic improvement nitrates should be up titrated to achieve the desirable effect.
The Role of Organic Nitrates in the Treatment of Heart Failure

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