Treatment with Hydralazine and Nitrates

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Hydralazine and Isosorbide Dinitrate in Heart Failure

- Hemodynamic effect.
- Nitrate tolerance.
- Nitrate resistance.
- When and How to use it.
Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

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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, 0.33 to 0.97]).

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*Participants in the African-American Heart Failure Trial (A-HeFT) are listed in the Appendix.
Effect of Hyd-N on LV Function

Massie B Am J Cardiol 1977
EFFECT OF VASODILATOR THERAPY ON MORTALITY IN CHRONIC CONGESTIVE HEART FAILURE

Results of a Veterans Administration Cooperative Study*

Jay N. Cohn, M.D., Donald G. Archibald, M.Phil., Susan Ziesche, R.N., Joseph A. Franciosa, M.D., W. Eugene Harston, M.D., Felix E. Tristani, M.D., W. Bruce Dunkman, M.D., William Jacobs, M.D., Gary S. Francis, M.D., Kathleen H. Flohr, M.D., Steven Goldman, M.D., Frederick R. Cobb, M.D., Pravin M. Shah, M.D., Robert Saunders, M.D., Ross D. Fletcher, M.D., Henry S. Loeb, M.D., Vincent C. Hughes, M.D., and Bonnie Baker, M.D.

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 HF.
Mean EF 30%, mean max VO2 14.5
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).
Primary end point -2 years all cause death
V-HeFT I Study
Effect on all cause mortality

Average Dose:
Hydralazine 270 mg/d
ISDN 136 mg/d

mortality reduction at 2 years 25% (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</td>
<td>Hyd–Iso</td>
<td>Placebo</td>
</tr>
<tr>
<td>1</td>
<td>273</td>
<td>186</td>
<td>19.5</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>147</td>
<td>34.3</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>108</td>
<td>46.9</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>70</td>
<td>53.6</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>36</td>
<td>—</td>
</tr>
</tbody>
</table>

Mortality reduction over the entire period: P=0.093 log rank test and 0.04 wilcoxon test
253 class IV HF patients randomized to placebo or enalapril
A COMPARISON OF ENALAPRIL WITH HYDRALENE–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., GEETHA 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 HAKENSON, 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.
Randomized to enalapril 20 mg/d or Hyd/ISDN 300/160 mg
Average dose 199/100 mg/d
Identical survival curves on Hyd/N in V-HeFT I and II

Figure 4. Survival Curve for the Hydralazine–Isosorbide Dinitrate Arm in the Earlier Trial (Solid Line) Superimposed on the Survival Curve for the Same Treatment Arm in the Current Trial (Dashed Line).
Change in EF and maximum oxygen consumption higher with nitrates

BP decrease 5/4 mmHg with enalapril and 0/1 mmHg with Hyd/ISDN

**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
1050 AA patients with HFrEF. NYHA III-IV. Randomly to a fixed dose Hyd/ISDN (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**

- **Standard Therapies + BiDiil**
  - Event rate = 16.4%
  - 39% Reduction*
  - $P < 0.001$ by Log-Rank Test

- **Standard Therapies + Placebo**
  - Event rate = 24.4%

*Statistical significance indicated.
## 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

*P<0.05  
†P<0.01

BiDil, n = 423  
Placebo, n = 441

MLHF® Questionnaire=Minnesota Living With Heart Failure® Questionnaire.
A-HeFT Results: **Additional 43% Reduction in Mortality** When Added to Current Standard Therapies

- **Standard Therapies + BiDil**
  - Event rate = 6.2%
  - 43% Reduction*
  - \( P = 0.012 \) by Log-Rank Test

- **Standard Therapies + Placebo**
  - Event rate = 10.2%

*Event rate = % of patients who experience the event (e.g., death) by a certain time point.
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
- 15% treated with Hyd-ISDN before the admission.
- Mortality at 18 months was 22% vs 25% (p=0.009) HR 0.85.
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
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

Figure 4
Change in Mean SBP in Baseline SBP Quartiles and in Baseline SBP ≤100 mm Hg
### Bidyl

#### What is the Dose?

<table>
<thead>
<tr>
<th>Daily Dose for Bidil</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Dose</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Dose</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduced Dose</strong>&lt;sup&gt;† ‡&lt;/sup&gt;</td>
<td><img src="https://example.com/bidyl-reduced-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-reduced-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-reduced-dose.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Starting Dose</strong>&lt;sup&gt;‡ ‡&lt;/sup&gt;</td>
<td><img src="https://example.com/bidyl-standard-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-standard-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-standard-dose.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Maximum Dose</strong>&lt;sup&gt;∥ ††&lt;/sup&gt; (if tolerated)</td>
<td><img src="https://example.com/bidyl-maximum-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-maximum-dose.png" alt="Image" /></td>
<td><img src="https://example.com/bidyl-maximum-dose.png" alt="Image" /></td>
</tr>
</tbody>
</table>

- Reduced Dose: 37.5 mg / 20mg
- Starting Dose: 75 mg / 40 mg
- Maximum Dose (if tolerated): 75 mg / 40 mg
Hydralazine / ISDN
What is the Dose?

## Daily Dose for Bidil

<table>
<thead>
<tr>
<th></th>
<th>1(^{st}) Dose</th>
<th>2(^{nd}) Dose</th>
<th>3(^{rd}) Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduced Dose(^{\dagger \dagger})</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Starting Dose(^{\dagger \dagger})</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Dose(^{\dagger \dagger \dagger})</strong></td>
<td>[\text{if tolerated}]</td>
<td>[\text{if tolerated}]</td>
<td>[\text{if tolerated}]</td>
</tr>
</tbody>
</table>

Mean dose in A-HeFT:
- Hydralazine 142 mg/d
- ISDN 76 mg/d
Why Use Hydralazine?

- Isosorbide dinitrate releases nitric oxide, dilates arteries and veins.
- Hydralazine HCl may also mitigate tolerance to nitrates, dilates arteries.
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.
6. Inhibition of sGC by superoxide and peroxynitrite.
7. Inactivation of cGMP
8. Inhibition of PGI-S

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

Superoxide production

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.67)
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.
# Adverse Effects

<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>
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</table>
DB, Placebo-Controlled Study of Organic Nitrates in Patients with Chronic HFrEF Treated With ACEI

**Figure 1.** Study design included a single-blind placebo stabilization period of 1 week and 2 periods of 12 weeks each in which patients were randomized and crossed over to receive transdermal NTG 50 to 100 mg for 12 h/d or transdermal placebo. The 2 treatment periods were separated by 4 weeks of a single-blind placebo washout period.

**Table 1. Baseline Variables in the 2 Study Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=14)</th>
<th>Group B (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48±3</td>
<td>48±4</td>
<td>0.87</td>
</tr>
<tr>
<td>Male, %</td>
<td>72</td>
<td>93</td>
<td>0.17</td>
</tr>
<tr>
<td>CHF duration, y</td>
<td>2.1±0.65</td>
<td>1.1±0.27</td>
<td>0.18</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24±3</td>
<td>26±2</td>
<td>0.61</td>
</tr>
<tr>
<td>Captopril dose, mg/d</td>
<td>106±20</td>
<td>88±11</td>
<td>0.38</td>
</tr>
<tr>
<td>Lasix dose, mg/d</td>
<td>80±13</td>
<td>103±22</td>
<td>0.38</td>
</tr>
<tr>
<td>Digoxin dose, mg/d</td>
<td>0.22±0.08</td>
<td>0.24±0.03</td>
<td>0.37</td>
</tr>
<tr>
<td>NTG dose, mg/d</td>
<td>54±5</td>
<td>59±4</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Group A includes patients receiving NTG as first drug; group B, patients receiving placebo as first drug.

Elkayam U et al Circulation 1999;99:2652-7
DB, Placebo-Controlled Study of Organic Nitrates in Patients with Chronic HFrEF Treated With ACEi

Figure 2. Change in treadmill exercise time from baseline 4 hours after administration of NTG (△) and placebo (○).

Figure 5. Percent change in LVEDD, LVESD, and fractional shortening (FS) from baseline after 3 months of therapy with NTG (solid bars) and placebo (open bars). *Statistically significant.

Elkayam et al. Circulation 1999;99;1652-7
Should Hyd/Nitrarare therapy be used in non AA patients?
Use of Hyd-N in non AA

- 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)*

- Pregnant women with symptomatic HF due to HFrEF.
Summary

- Hyd/ISDN combination (Bidil) is one of the most effective and underutilized interventions for the treatment of AA patients with symptomatic HFrEF.

- Use of Hyd/ISDN is recommended to all patients not tolerating angiotensin blocking therapy regardless of race.
Hydralazine improves hemodynamic effect and also prevents attenuation of nitrates effect due to tolerance.
The Role of Organic Nitrates in the Treatment of Heart Failure

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