Vasodilator Therapy In Chronic Heart Failure

Uri Elkayam, MD
Professor of Medicine
University of Southern California
School of Medicine
Los Angeles, California
elkayam@usc.edu
Jonathan Abrams, MD

A Legacy of Medicine And Art
Hydralazine and Isosorbide Dinitrate in Heart Failure

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

Am J Cardiol 1977
Hemodynamic Effects of Hydralazine/Nitrate Combination

Roth, Elkayam AHJ 1993;125:155
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.)
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 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.
A COMPARISON OF ENALAPRIL WITH HYDRALAZINE–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 Haakenson, 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.)
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.
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
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
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, 0.39 to 0.82]; 17 percent reduction in the rate of hospitalization for heart failure [hazard ratio, 0.83; 0.67 to 1.01]; and 17 percent decrease in the rate of change in quality of life [hazard ratio, 0.83; 0.71 to 0.97]).

From the University of Minnesota (A.L.T., J.N.C.) and Minneapolis Veterans Affairs Hospital (S.Z.) — both in Minneapolis; University of Texas Southwestern Medical Center, Dallas (C.Y.); Veterans Affairs Medical Center, Washington, D.C. (P.C.); Wake Forest University, School of Medicine, Winston-Salem, N.C. (R.D.); Heartbeats Life Center and Xavier University, New Orleans (K.F.); Jackson Cardiology Associates, Jackson, Miss. (M.T.); Association of Black Cardiologists, Atlanta (M.T.); University of North Carolina, Chapel Hill (K.A.); and NitroMed, Lexington, Mass. (M.S., M.W.).

Address reprint requests to Dr. Anne Taylor at the Department of Medicine/Cardiology, University of Minnesota Medical School, 420 Delaware St. SE, MMC 293, Minneapolis, MN 55455, or at taylor135@umn.edu.

*Participants in the African-American Heart Failure Trial (A-HeFT) are listed in the Appendix.
ABSTRACT

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.

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,
A-HeFT Results: Additional 39% Risk Reduction in First Hospitalization for Heart Failure When Added to Current Standard Therapies

- Standard Therapies + BiDiL: Event rate = 16.4%
- Standard Therapies + Placebo: Event rate = 24.4%

*P < 0.001 by Log-Rank Test
# 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>BiDil, n = 423</th>
<th>Placebo, n = 441</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>369</td>
<td>371</td>
</tr>
<tr>
<td>6</td>
<td>307</td>
<td>305</td>
</tr>
<tr>
<td>9</td>
<td>269</td>
<td>250</td>
</tr>
<tr>
<td>12</td>
<td>226</td>
<td>218</td>
</tr>
<tr>
<td>15</td>
<td>198</td>
<td>184</td>
</tr>
<tr>
<td>18</td>
<td>512</td>
<td>528</td>
</tr>
</tbody>
</table>

MLHF® Questionnaire=Minnesota Living With Heart Failure® Questionnaire.

*P<0.05
†P<0.01
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%

Survival (%) vs. Time (days)
Effect on Mortality of Various HF Medications

**Absolute Mortality (%)**

- **ACE-Ils**
  - Placebo: 21.9%
  - Drug: 15.8%
  - Decrease: 23%

- **β-Blockers**
  - Placebo: 18.0%
  - Drug: 13.3%
  - Decrease: 26.1%

- **BiDil**
  - Placebo: 10.2%
  - Drug: 6.2%
  - Decrease: 43%

---

### 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

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

Figure 1. Kaplan-Meier Estimates of Death from Any Cause.
CI denotes confidence interval.

Figure 1. Kaplan-Meier Estimates of Overall Survival.

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*

AHA/ACC 2013 Practice Guideline
## 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</strong></td>
<td><img src="chart.png" alt="Red Dose" /></td>
<td><img src="chart.png" alt="Red Dose" /></td>
<td><img src="chart.png" alt="Red Dose" /></td>
</tr>
<tr>
<td><strong>Starting Dose</strong></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
</tr>
<tr>
<td>37.5 mg / 20mg</td>
<td><img src="chart.png" alt="Red Dose" /></td>
<td><img src="chart.png" alt="Red Dose" /></td>
<td><img src="chart.png" alt="Red Dose" /></td>
</tr>
<tr>
<td><strong>Maximum Dose</strong> (if tolerated)</td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
</tr>
<tr>
<td>75 mg / 40 mg</td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
<td><img src="chart.png" alt="Orange Dose" /></td>
</tr>
</tbody>
</table>
### Hydralazine / ISDN

#### What is the Dose?

<table>
<thead>
<tr>
<th>Daily Dose for Bidil</th>
<th>1\textsuperscript{st} Dose</th>
<th>2\textsuperscript{nd} Dose</th>
<th>3\textsuperscript{rd} Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Dose(\dagger\ II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting Dose(\dagger\ II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Dose(\dagger\dagger\dagger) (if tolerated)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean dose in A-HeFT: Hydralazine 142 mg/d
ISDN 76 mg/d
Protocol For The Use Of Hyd/ISDN In The Hospital

**Isosorbide dinitrate**

- Begin 10 mg orally
- After 2 h, if initial dose tolerated, ↑ to 20 mg
- After 8 h, if 20 mg tolerated, ↑ to 40 mg
- After 8 h, if 40 mg tolerated, ↑ to 60 mg
- After 8 h, if 60 mg tolerated, then 60 mg orally TID*

**Hydralazine**

- Begin 25 mg orally (or 10 mg if MAP is low or patient is in labile condition)
- After 2 h, if initial dose tolerated, ↑ to 50 mg
- After 6 h, if 50 mg tolerated, ↑ to 75 mg
- After 6 h, if 75 mg tolerated, ↑ to 100 mg
- After 6 h, if 100 mg tolerated, then 100 mg QID*
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.
The initial dose was 1 pill of bidil equals 37.5 mg hydralazine and 20 mg of ISDN.

Target dose was 75 mg tid of hydralazine (225 mg/d) and 40 mg tid of ISDN (120 mg/d).

Mean dose was 142 mg/d of hydralazine and 76 mg of ISDN.
Why Use Hydralazine?

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

- **Hydralazine HCl**
  - May also mitigate tolerance to nitrates
  - Dilates arteries
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.
Consequences of Nitric Oxide and Super Oxide Balance Disruption in Heart Failure Patients

Despite proven benefits, combination hydralazine and nitrate therapy is not commonly used in HF.
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
Effect of baseline BP on morbidity and mortality


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>
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

24% survival benefit with ICD in 45 months

43% improvement in survival in 10 months
P=0.01

Figure 1. Kaplan–Meier Estimates of Overall Survival.

Figure 1. Kaplan–Meier Estimates of Death from Any Cause.
CI denotes confidence interval.

SCD - HeFT

A - HeFT
Can the combination therapy be used in non AA patients?
A combination of hydralazine and isosorbide dinitrate 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, unless contraindicated. *(Level of Evidence: B)*
Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered.
A COMPARISON OF ENALAPRIL WITH HYDRAZINE–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 Haakenson, 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 in 804 medical inpatients with congestive heart failure. A double-blind randomized study was performed in 300 mg of hydralazine daily for 8 weeks. The latter similar patients were in our previous Vasodilator therapy for congestive heart failure (18 percent) mortality in the hydralazine arm was lower than in the placebo arm (25 percent, 18 percent) mortality in the hydralazine–isosorbide dinitrate 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, reflecting the 2 years the treatment was given, was 0.55 (P < 0.05) during hydralazine–isosorbide dinitrate therapy. 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.)
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

Log Rank, p = 0.004

Freedom from mortality and hospitalizations

Log Rank, p = 0.003
Nitrates in patients with HFrEF in the CHAMPION study

Increased furosemide dose by 51 mg/d.

Increased nitrates dose by 18 mg/d.
Summary

- 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.
- 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.
The Role of Organic Nitrates in the Treatment of Heart Failure

Uri Elkayam, MD
Professor of Medicine
University of Southern California
School of Medicine
Los Angeles, California
elkayam@usc.edu