Impact of the African American Heart Failure Trial (A-HeFT): Guideline-based Therapy in Blacks with Heart Failure 2016

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Keith C. Ferdinand, MD

Has disclosed the following affiliations. Any real or apparent COIs related to the presentation have been resolved.

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Consultant
- Amgen, Sanofi, Boehringer Ingleheim, Eli Lilly

Stocks - None

Patents - None
<table>
<thead>
<tr>
<th>Trial</th>
<th>Rx</th>
<th>Total</th>
<th>Non-African Americans</th>
<th>African Americans</th>
<th>African Americans (%)</th>
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<tbody>
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<td>V-HeFT I + II</td>
<td>ISDN/HYD, Enalapril</td>
<td>1419</td>
<td>1024</td>
<td>395</td>
<td>28</td>
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<td>SOLVD</td>
<td>Enalapril</td>
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<td>2175</td>
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<td>US Carvedilol</td>
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<td>2081</td>
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<td>MERIT-HF</td>
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<td>3783</td>
<td>208</td>
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<td>EPHESUS</td>
<td>Eplerenone</td>
<td>6632</td>
<td>6558</td>
<td>74</td>
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<td>Val-HeFT</td>
<td>Valsartan</td>
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<td>4666</td>
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<td>7</td>
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<td>VALIANT</td>
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<td>14703</td>
<td>14296</td>
<td>407</td>
<td>3</td>
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<td>CHARM</td>
<td>Candesartan</td>
<td>3023</td>
<td>2897</td>
<td>126</td>
<td>4</td>
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<tr>
<td>A-HeFT</td>
<td>ISDN/HYD</td>
<td>1050</td>
<td>1050</td>
<td>1000</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>44,488</td>
<td>40,525</td>
<td>3,963</td>
<td>7</td>
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</tbody>
</table>

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*
Mechanism of Action: Fixed-dose combination ISDN/HYD

Isosorbide dinitrate (ISDN)
- Large and small artery dilator
- Venous dilator
- Nitric oxide donor

Hydralazine HCl (HYD)
- Arteriolar dilator

Fixed-dose combination ISDN/HYD
(20 mg and 37.5 mg, respectively, per tablet)
A-HeFT Trial Summary

- N=1,050 AA HF, NYHA Class III-IV\(^1,2\)
  - 70% on ACE-I
  - 17% on ARB
  - Approx. 75% on β-blocker
- Titration goal 2 tablets tid = 225 mg ISDN/HYD
- Primary endpoint: combined score of mortality, hospitalization, and QOL
- Terminated 7/19/04 for significant survival benefit in FD ISDN/HYD group

QOL, quality of life

A-HeFT Inclusion Criteria

- Self-identified African American (black) patients
- Symptomatically stable NYHA Class III-IV
- On standard HF treatment
  - If on β-blockers, treated for at least 3 mo prior to study entry
- Ejection fraction
  - LVEF ≤35% or
  - LVEF <45% with resting LVIDD >2.9 cm/m² (or >6.5 cm)

# A-HeFT Baseline Characteristics

<table>
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<tr>
<th></th>
<th>FD ISD/HYD n = 518</th>
<th>Placebo n = 532</th>
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<tbody>
<tr>
<td><strong>Age (mean), yr</strong></td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>56%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>IV</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Primary cause of heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40%</td>
<td>37%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* $P < 0.05$
A-HeFT Primary Endpoint

 Composite score
 – All-cause mortality
 – First HF hospitalization
 – Change in QoL at 6 mo relative to baseline
AHeFT: Trial Summary  N=1050

All-Cause Mortality (%)

- Placebo + Standard Therapies: n=54, 10.2%
- HYD/ISDN + Standard Therapies: n=32, 6.2%

First HF Hospitalization (%)

- Placebo + Standard Therapies: n=130, 24.4%
- HYD/ISDN + Standard Therapies: n=85, 16.4%

Patient Reported Functional Status

- Placebo + Standard Therapies: n=532
e vs HYD/ISDN + Standard Therapies: n=518

P=0.012
P<0.001
P<0.01

A-HeFT: All-Cause Mortality

Fixed-dose Hydralazine/Isosorbide Dinitrate

Survival (%)

Hazard ratio = .57

Placebo 43% Decrease

P = .01

Days Since Baseline Visit Date

Fixed-dose I/H 518 463 407 359 313 251 13

Placebo 532 466 401 340 285 232 24

MINI-FOCUS ISSUE: PHARMACOGENETICS AND PERSONALIZED MEDICINE

CLINICAL RESEARCH

G-Protein Beta-3 Subunit Genotype Predicts Enhanced Benefit of Fixed-Dose Isosorbide Dinitrate and Hydralazine
Results of A-HeFT

Dennis M. McNamara, MD, MS,* Anne L. Taylor, MD,† S. William Tam, PhD,‡ Manuel Worcel, MD,§ Clyde W. Yancy, MD, MSc,|| Karen Hanley-Yanez, BS,* Jay N. Cohn, MD,¶ Arthur M. Feldman, MD, PhD#

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the influence of the guanine nucleotide-binding proteins (G-proteins), beta-3 subunit (GNB3) genotype on the effectiveness of a fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in A-HeFT (African American Heart Failure Trial).

BACKGROUND GNB3 plays a role in alpha₂-adrenergic signaling. A polymorphism (C825T) exists, and the T allele is linked to enhanced alpha-adrenergic tone and is more prevalent in African Americans.

METHODS A total of 350 subjects enrolled in the genetic substudy (GRAHF [Genetic Risk Assessment of Heart Failure in...
<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><strong>43</strong></td>
<td><strong>7</strong></td>
<td><strong>33</strong></td>
</tr>
</tbody>
</table>
The combination of HYD and ISDN is recommended for African Americans with NYHA class III–IV HFrEF on GDMT IA.

A combination of HYD and ISDN can be useful with HFrEF who cannot be given ACE-Is or ARBs IIa B.

Primary HF Therapies for Blacks Prior to the A-HeFT

Heart

β-blockers

ACE-Is, ARBs

Diuretics

Peripheral arteries

Kidney

Standard Care Treatment post-Aheft should include FDC of ISDN/HYD

A-HeFT: Conclusions

- Fixed-dose ISDN/HYD benefits African American HF patients on neurohormonal blockers:
  - Increases survival 43%
  - Decreases first hospitalization for HF 33%
  - Improves QOL
  - Nitric oxide enhancing therapy a novel and highly effective HF therapy
Thank You!