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Associate Dean of Clinical Research
Director, Clinical Research Center

Treatment of Heart Failure in African Americans
Learning Objectives

- Epidemiology of Heart Failure in African-Americans
- African-American Heart Failure Trial
- ACC/AHA Guidelines
- Bioequivalence
- Summary
Heart Failure: A Major Economic Burden in the United States

- HF is the most common Medicare DRG\(^1\)
  - Accounts for more Medicare dollars vs. all other diagnosis

- Hospital discharges for HF rose from 377,000 in 1979 to 970,000 in 2002, an increase of 157\(^2\)

- The estimated direct and indirect costs of HF in the US are $27.9 billion for 2005\(^2\)
  - >5.4% of the U.S. health care budget, since 1991

Heart Failure in African Americans

- Estimated U.S. prevalence of heart failure (HF) among African Americans (AAs) is 900,000

- 4.2% of AA population versus 2.4% of Caucasian population (5.4 million)

- Likelihood of developing HF before age 50 is 20 times higher (p=0.001) among AAs versus Caucasians

- Age of onset is significantly earlier among AAs versus other racial/ethnic groups (63.8 vs 70.8 years, p=0.003)

Heart Failure in African Americans

Prognosis is poorer for AAs versus Caucasians

- 2.5 times greater risk of HF-related mortality among AAs with HF aged 45-64 vs. similarly-aged Caucasians with HF
- 1.8 times higher mortality among AA men versus Caucasian men
- 2.4 times higher among AA women versus Caucasian women
- 42% higher risk for HF-related hospitalization

Mechanisms of disease and responses to pharmacologic therapy among AAs may differ from those of Caucasians

Progression from Hypertension to Heart Failure

Obesity
Diabetes
Insulin Resistance

HTN
Smoking
Lipids
Diabetes

Normal Left Ventricular (LV) Structure and Function

LVH
MI

LV Remodeling

Diastolic Dysfunction

Subclinical LV Dysfunction

Systolic Dysfunction

CHF
Overt HF
Death

Time (decades)

Time (months)

Etiology of HF in Clinical Trials

% of Patients With Coronary Artery Disease-Based HF

% of Patients With Hypertension-Based HF

Etiology of Heart Failure in Black Patients

LVH=left ventricular hypertrophy.
Adapted from Yancy CW. J Card Fail. 2003;9(suppl 5):S210-S215.
Cumulative incidence of HF by hypertension stage

Framingham Heart Study

Cumulative incidence of CHF (%)

Years from baseline exam

Stage 2+ ($\geq 160/\geq 100$ mm Hg$^*$)
Stage 1 (140–159/90–99 mm Hg$^\dagger$)
Normal BP

*Or current use of antihypertensive medication
†And not receiving antihypertensive medication

NHLBI. Congestive Heart Failure Data Fact Sheet. 2004.
Cardiovascular Risk Factors & Co-morbidities in Heart Failure Patients

- **HTN**: 98%
- **LVH**: 61%
- **Uncontrolled HTN**: 59%
- **CAD**: 52%
- **DM**: 42%
- **ETOH Abuse**: 22%

Uncontrolled hypertension and LVH associated with increased HF hospitalization.

Age ± 64 yrs
N=1200
98% AAs

Ofili EO et al. Am J Cardiol 1999;83:1350
Clinical response of black patients with hypertension to ACEs showed **differing responses** from those of white patients.

A re-analysis of the data from the V-HeFT trials to **assess differences** in racial response to specific therapies within these studies.¹

The analysis was **started with V-HeFT II** because it included an ACE arm.¹

The retrospective analysis of V-HeFT I & II suggested that individual components of Isosorbide Dinitrate (ISDN) and Hydralazine (HYD) may be beneficial in black patients with HF, based on consistent, positive trends.

It was suggested that a prospective trial among black HF patients was needed to systematically study the hypothesis generated by his retrospective analysis.

The African-American Heart Failure Trial (A-HeFT): Demonstrated Results
A-HeFT: 43% Decrease in Mortality

- Fixed-dose I/H
  - Days Since Baseline Visit Date: 518, 463, 407, 359, 313, 251, 13
- Placebo
  - Days Since Baseline Visit Date: 532, 466, 401, 340, 285, 232, 24

Hazard ratio = 0.57
P = 0.01

Taylor AL et al. NEJM 2004; 351:2049-2057
## A-HeFT: Baseline HF Medications

<table>
<thead>
<tr>
<th></th>
<th>Fixed-dose I/H (N=518)</th>
<th>Placebo (N=532)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% of Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>ARB</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Digoxin</td>
<td>59</td>
<td>61</td>
</tr>
</tbody>
</table>

Taylor AL et al. NEJM 2004; 351:2049-2057
A-HeFT Results: Significant Improvement in All Components of Composite Score With FDC-I/H

**All-Cause Mortality (%)**
- Standard Therapies + Placebo: 6.2 (n=32)
- Standard Therapies + FDC-I/H: 10.2 (n=54)
- P=0.012

**First HF Hospitalization (%)**
- Standard Therapies + Placebo: 24.4 (n=130)
- Standard Therapies + FDC-I/H: 16.4 (n=85)
- P<0.001

**Change in Patient-Reported Functional Status**
- n=518 (Standard Therapies + Placebo)
- n=532 (Standard Therapies + FDC-I/H)
- P<0.01

Patient-reported functional status was assessed by responses to the Minnesota Living With Heart Failure® Questionnaire.

Taylor AL et al. NEJM 2004; 351:2049-2057
A-HeFT: Significant Additional Improvement In Functional Status

Change in MLHF® Questionnaire Score

Time (months)

FDC(BiDil), n = 423
Placebo, n = 441

MLHF® (Minnesota Living with Heart Failure)
A-HeFT: Improvement in Patient Functional Status

- Quality of life measures in A-HeFT were assessed by means of the Minnesota Living with Heart Failure questionnaire, a 21-question self-administered instrument.

- The FDC-I/H treated group had statistically significant improvement in response to the Minnesota Living with Heart Failure questionnaire, a self-report of patient’s functional status, at most time points.
## Baseline Echocardiogram Measurements

<table>
<thead>
<tr>
<th></th>
<th>FDC I/H (n)</th>
<th>Placebo (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>35.5 ± 9.2 (329)</td>
<td>34.5 ± 9.3 (337)</td>
</tr>
<tr>
<td>LVIDD (cm)</td>
<td>6.18 ± 1.4 (337)</td>
<td>6.3 ± 1.5 (341)</td>
</tr>
<tr>
<td>LVIDD/BSA (cm/m²)</td>
<td>3.06 ± 0.8 (335)</td>
<td>3.01 ± 0.75 (336)</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>106.6 ± 41.2 (329)</td>
<td>112.6 ± 64.8 (337)</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>70.8 ± 34.5 (329)</td>
<td>75.2 ± 41.7 (337)</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>134.5 ± 62.6 (337)</td>
<td>139.4 ± 85.6 (341)</td>
</tr>
<tr>
<td>LV systolic sphericity index</td>
<td>0.54 ± 0.15 (325)</td>
<td>0.55 ± 0.016 (332)</td>
</tr>
<tr>
<td>LV diastolic sphericity index</td>
<td>0.59 ± 0.14 (325)</td>
<td>0.59 ± 0.15 (332)</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; LVIDD, internal dimension at end-diastole; BSA, body surface area; LVEDVᵢ, end-diastolic volume index; LVESVᵢ = end-systolic volume index.

* No significant difference between groups.
Kaplan-Meier survival curves in the echo cohort of African-American Heart Failure Trial.

Isosorbide Dinitrate and Hydralazine in a Fixed-Dose Combination Produces Further Regression of Left Ventricular Remodeling in a Well-Treated Black Population With Heart Failure: Results From A-HeFT

Jay N. Cohn, S. William Tam, Inder S. Anand, Anne L. Taylor, Michael L. Sabolinski, Manuel Worcel

Journal of Cardiac Failure Volume 13, Issue 5 2007 331 - 339
Kaplan-Meier event-free survival curves in the echo cohort of African-American Heart Failure Trial.

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Kaplan-Meier event-free survival curves in the echo cohort of African-American Heart Failure Trial by changes in left ventricular ejection fraction from baseline at 6 months.

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Kaplan-Meier event-free survival curves in the echo cohort of African-American Heart Failure Trial by increase or decrease in internal dimension at end-diastole from baseline at 6 months.

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Journal of Cardiac Failure Volume 13, Issue 5 2007 331 - 339
Changes of left ventricular ejection fraction and internal dimension at end-diastole from baseline at 6 months.

Results represent mean +/- SEM.

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Journal of Cardiac Failure Volume 13, Issue 5 2007 331 - 339
Baseline, Month 6, and Change from Baseline Plasma BNP Concentrations in A-HeFT

<table>
<thead>
<tr>
<th></th>
<th>FDC I/H (n = 343)</th>
<th>Placebo (n = 340)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>283 ± 365</td>
<td>332 ± 446</td>
<td>0.15</td>
</tr>
<tr>
<td>Month 6</td>
<td>243 ± 347</td>
<td>324 ± 444</td>
<td>0.005</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>39 ± 305</td>
<td>8 ± 365</td>
<td>0.05</td>
</tr>
</tbody>
</table>

2-sample t-test on Ln(BNP).
Endothelial Nitric Oxide Synthase (NOS3) Polymorphisms in African Americans With Heart Failure: Results From the A-HeFT Trial

Racial differences in NOS3 alleles: genotype frequencies for the NOS3 polymorphisms in the white heart failure cohort in Genetic Risk Assessment of Cardiac Events (GRACE) and the African-American heart failure cohort from Genetic Risk Assessment..

Dennis M. McNamara, S. William Tam, Michael L. Sabolinski, Page Tobelmann, Karen Janosko, Lakshmi Venkitachal, Elizabeth Ofili....

Journal of Cardiac Failure Volume 15, Issue 3 2009 191 - 198
Interaction of NOS3 Glu298Asp polymorphisms on the impact of therapy with fixed-dose combination of isosorbide dinitrates and hydralazine (FDC I/H) on outcomes. (A) Effect on composite score: treatment associated with improvement in the Glu...

Dennis M. McNamara, S. William Tam, Michael L. Sabolinski, Page Tobelmann, Karen Janosko, Lakshmi Venkitachal, Elizabeth Ofili…

Journal of Cardiac Failure Volume 15, Issue 3 2009 191 - 198
Consequences of Nitric Oxide and Super Oxide Balance Disruption in Heart Failure Patients

ACC/AHA Guidelines
Heart Failure Treatment Guidelines – Recommend FDC-I/H

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) 2009 Focused Update to the Practice Guidelines for the Diagnosis and Management of Heart Failure in Adults.

FDC-I/H is a Class 1 recommendation (i.e., procedure/treatment should be administered) to improve outcomes for patients self-described as African-American with moderate to severe symptoms of heart failure.

Guideline emphasizes that HF in blacks occurs at a higher incidence, at an earlier age, and progresses more rapidly than white patients - warranting a more aggressive approach.

Guideline also refers to a prospective, double blind randomized trial in black patients and it is important to realize that this study was A-HeFT.

The Guidelines update to include fixed dose (FDC-I/H) was driven by the outcomes of the A-HeFT.

Note that the “proprietary formulation” of fixed-dose of (FDC-I/H) used in A-HeFT was BiDil.

ACC/AHA Class 1 Recommendation

Treatment of Special Populations

• The use of a fixed dose combination of hydralazine and isosorbide dinitrate in self-identified African-Americans.

• The combination of a fixed dose of isosorbide dinitrate and hydralazine to a standard medical regimen for heart failure, including ACE Inhibitors and beta-blockers, is recommended in order to improve outcomes for patients self-described as African Americans, with NYHA functional class III or IV HF.

• Modified recommendation based on A-HeFT (African American Heart Failure Trial) and robust secondary analyses of the original database all confirm a substantial benefit for African Americans with heart failure.

Bioequivalence
Bioequivalence Determination

FDA Definition of Bioequivalence

“…the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses…”
“Approval of a generic version of a proprietary drug by the FDA requires demonstration of … “bioequivalence” (defined by absorption parameters generally falling between 80% and 125% of those obtained with the proprietary agent under the same testing conditions). The use of the -20%+/+25% rule is based on a regulatory decision that for most drugs that difference in concentration of the active ingredient in blood will not be clinically significant.”
Bioequivalence Determination

Review of PK Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tablet</th>
<th>Percent Relative to BiDil Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDC-I/H</td>
<td>Tablet</td>
<td>45%*</td>
</tr>
<tr>
<td>INDIVIDUAL Hydralazine</td>
<td>Tablet</td>
<td>29%*</td>
</tr>
<tr>
<td>FDC-I/H</td>
<td>Tablet</td>
<td>100%</td>
</tr>
<tr>
<td>INDIVIDUAL ISDN</td>
<td>Tablet</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Cmax* represents percent relative difference in Cmax levels.

† Cmax = Maximum plasma concentration in the body. Adapted from Tam, et al 2007; 46 (10): 885-895. n=56
“FDA has not approved any drug product under Section 505 of the Federal Food, Drug, and Cosmetic Act that is designated as therapeutically equivalent (i.e. substitutable) to BiDil. In addition, neither approved labeling for isosorbide dinitrate drug products nor approved labeling for hydralazine hydrochloride drug products contains information regarding the use of these drug products for the treatment of heart failure.”
Adverse Reactions

Headache and dizziness were the most frequent adverse events occurring at an incidence greater than 2% in clinical studies compared to placebo. Others included chest pain, asthenia, nausea, bronchitis, hypotension, sinusitis, ventricular tachycardia, palpitations, hyperglycemia, rhinitis, paresthesia, vomiting, amblyopia, hyperlipidemia, and tachycardia.
• Treatment with hydralazine hydrochloride may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis. If systemic lupus erythematosus-like symptoms occur in patients treated with BiDil, discontinuation of BiDil should be considered only after a thorough benefit-to-risk assessment. Symptoms and signs of systemic lupus erythematosus usually regress when hydralazine hydrochloride is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

• Hydralazine hydrochloride has been associated with peripheral neuritis, evidenced by paresthesia, numbness, and tingling, which may be related to an antipyridoxine effect. Pyridoxine should be added to BiDil therapy if such symptoms develop.

• Isosorbide dinitrate therapy may aggravate angina associated with hypertrophic cardiomyopathy.

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Overview of HF Management

At Risk for Heart Failure

Stage A
At high risk for HF but without structural heart disease or symptoms of HF.

- Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes
  - Metabolic syndrome
  - Patients using cardiotoxins with HFx CM

Stage B
Structural heart disease but without symptoms of HF.

- Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

Stage C
Structural heart disease with prior or current symptoms of HF.

- Patients with:
  - Known structural heart disease
  - Shortness of breath and fatigue, reduced exercise tolerance

Stage D
Refractory HF requiring specialized interventions.

- Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Therapy Goals
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

Drugs
- ACEI or ARB in appropriate patients (see text)
- Beta-blockers in appropriate patients (see text)

Devices in Selected Patients
- Implantable defibrillators

Therapy Goals
- All measures under stages A and B
- Dietary salt restriction
- Drugs for Routine Use
- Diuretic for fluid retention
- ACEI
- Beta-blockers

Drugs in Selected Patients
- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates

Devices in Selected Patients
- Biventricular pacing
- Implantable defibrillators

Therapy Goals
- Appropriate measures under stages A, B, C
- Decision re: appropriate level of care

Options
- Compassionate end-of-life care/hospice
- Extraordinary measures
- Heart transplant
- Chronic inotropes
- Permanent mechanical support
- Experimental surgery or drugs

Morehouse School of Medicine
#1 in Social Mission among US medical schools (Annals of Internal Medicine, June 2010)

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Thank you!!!!