Pharmacogenomics of Heart Failure in African Americans

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Disclosures

• Research Support ongoing (GRAHF2):
  - NIMHD (R01MD009118)
  - Arbor Pharmaceutical

• Research Support (past):
  - Nitromed (AHeFT and the genetic sub-study, GRAHF)
Case: Presentation

- 50 year old man with two months exertional dyspnea. No chest pain. NYHA class 3 limitations.

- On exam BP 110/70, HR 88, clear lungs, S4 no murmurs, no JVD and no peripheral edema

- Echocardiogram LVEF 30%, LVEDD 6.5 cm, mild hypertrophy, no valvular abnormalities. Nuclear stress no ischemia no scar.
Case: Which Therapy?

- ACE inhibitors
- beta blockers
- hydralazine/isosorbide dinitrates
- Aldosterone receptor antagonists

- One, two or all four?
- What order?
- How are patient outcomes, satisfaction, compliance impacted by polypharmacy?
Should All Therapies be Given to All Patients?

Drugs which improve outcomes for populations with heart failure may not be effective for an individual.
Heart Failure: Differences between African American and white cohorts

- Heart Failure Phenotype
- Clinical Outcomes
- Therapeutic Efficacy
Etiology of HF in African Americans

% of Patients With Coronary Artery Disease-Based HF

% of Patients With Hypertension-Based HF

V-HeFT I  V-HeFT II  SOLVD  US Carv  BEST  MERIT-HF

% AA  % non-AA
Impact of I/H versus placebo (VHeFT I) or ACEi (VHeFT II) by Race

**V-HeFT I**

- **Whites**
  - n = 324
  - $P = 0.47$
  - RR 12%

- **Blacks**
  - n = 128
  - $P = 0.04$
  - RR Reduction 47%

**V-HeFT II**

- **Whites**
  - n = 574
  - $P = 0.02$
  - RR Reduction 32%

- **Blacks**
  - n = 215
  - $P = 0.96$

Survival in A-HeFT

Fixed-dose isosorbide dinitrate plus hydralazine (ISDN/HYD)

Placebo

Hazard ratio = 0.57
P = .01

Days Since Baseline Visit

Survival (%)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>ISDN/HYD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days Since Baseline Visit</td>
<td>Number at risk</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>518</td>
<td>532</td>
</tr>
<tr>
<td>100</td>
<td>463</td>
<td>466</td>
</tr>
<tr>
<td>200</td>
<td>407</td>
<td>401</td>
</tr>
<tr>
<td>300</td>
<td>359</td>
<td>340</td>
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<tr>
<td>400</td>
<td>313</td>
<td>285</td>
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<tr>
<td>500</td>
<td>251</td>
<td>232</td>
</tr>
<tr>
<td>600</td>
<td>13</td>
<td>240</td>
</tr>
</tbody>
</table>

A-HeFT Genetic Sub-study

GRAHF

Genetic Risk Assessment in Heart Failure in African Americans
norepinephrine -> Renal $\beta_1$ receptor

$\beta_1$Arg389

Renin release

ACE inhibitor

$\text{ACE D/I}$

ARB

CYP11B2 T/C

Aldo receptor antagonists
norepinephrine

Renal $\beta_1$ receptor

Renin release

A II

Aldosterone

Beta blockers

ACE inhibitors

ARB

Aldo receptor antagonists

$\beta_1$Arg389

GNB3 T/C

ACE D/I

ISDN-HYD

CYP11B2 T/C
- ACE D/I
- Aldosterone synthase promoter

- NOS 3: Glu298Asp
- NOS 3: promoter 786
- NOS 3: intron 4

- β1 Gly389Arg
- β1 Ser49Gly
- β2 Gly16Gln
- β2 Gly27Gln
- β2 Thr164Ile

- alpha2C deletion
- GNB3 T825C
GRAHF: Different allele frequencies in Black and White cohorts

- ACE D/I
- Aldosterone synthase promoter
- NOS 3: Glu298Asp
- NOS 3: promoter 786
- NOS 3: intron 4
- \( \beta_1 \) Gly389Arg
- \( \beta_1 \) Ser49Gly
- \( \beta_2 \) Gly16Gln
- \( \beta_2 \) Gly27Gln
- \( \beta_2 \) Thr164Ile
- alpha2C deletion
- GNB3 T825C
## GRAHF subset of A-HeFT

<table>
<thead>
<tr>
<th></th>
<th>A-HeFT</th>
<th>GRAHF</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>1050</td>
<td>350</td>
</tr>
<tr>
<td>Age</td>
<td>56.8</td>
<td>57.4</td>
</tr>
<tr>
<td>% Male</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>% ischemic</td>
<td>23.0</td>
<td>26.3</td>
</tr>
<tr>
<td>% NYHA class III</td>
<td>95.7</td>
<td>96.8</td>
</tr>
<tr>
<td>Qualifying LVEF</td>
<td>24.1</td>
<td>24.0</td>
</tr>
<tr>
<td>% Deaths</td>
<td>8.2</td>
<td>3.4</td>
</tr>
<tr>
<td>% Hospitalization</td>
<td>20.5</td>
<td>16.7</td>
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</table>
GNB3 T825C polymorphism

• Alpha-2 adrenergic signaling occurs via specific heterotrimeric G-proteins including the G-protein β3 subunit (GNB3)

• A common C825T polymorphism exists for GNB3, with the T allele linked with enhanced alpha receptor intracellular signalling.

• The “T-allele” is also linked to hypertension and low plasma renin, and has a much higher prevalence in black cohorts than among whites.
The GNB3 C825T of exon 10 is functionally silent, but is tightly linked to a splicing variant of exon 9. The “T haplotype” has a truncated subunit which exhibits increased adrenergic signalling. Rosskopf et al. Hypertension 2000 (36) 33-41
Distribution of GNB3 genotypes by RACE: A-HeFT and GRACE

Comparison of allele distribution by race, T allele more prevalent in blacks, p <0.001

mcnamara et al, JACC-HF 2014
**GRAHF : Genetic Sub-study of AHeFT**  
Baseline Characteristics by GNB3 Genotype

<table>
<thead>
<tr>
<th></th>
<th>All (N=350)</th>
<th>TT (N=184)</th>
<th>TC+CC (N=166)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 13</td>
<td>57 ± 12</td>
<td>58 ± 13</td>
<td>0.699</td>
</tr>
<tr>
<td>Female (%)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>0.930</td>
</tr>
<tr>
<td>NYHA Class (%/III/IV)</td>
<td>97/3</td>
<td>97/3</td>
<td>97/3</td>
<td>0.894</td>
</tr>
<tr>
<td>Ischemic (%)</td>
<td>25</td>
<td>24</td>
<td>26</td>
<td>0.755</td>
</tr>
<tr>
<td>LVEF qualifying</td>
<td>0.25 ± 0.08</td>
<td>0.25 ± 0.08</td>
<td>0.24 ± 0.09</td>
<td>0.137</td>
</tr>
<tr>
<td>BP systolic</td>
<td>127 ± 17</td>
<td>128±16</td>
<td>126±17</td>
<td>0.290</td>
</tr>
<tr>
<td>BP diastolic</td>
<td>77 ± 10</td>
<td>77 ±10</td>
<td>76±11</td>
<td>0.520</td>
</tr>
<tr>
<td>ACE Inhibitor (%)</td>
<td>76</td>
<td>76</td>
<td>76</td>
<td>0.743</td>
</tr>
<tr>
<td>Aldosterone receptor antagonist</td>
<td>36</td>
<td>35</td>
<td>37</td>
<td>0.782</td>
</tr>
<tr>
<td>Beta Blocker (%)</td>
<td>84</td>
<td>85</td>
<td>83</td>
<td>0.569</td>
</tr>
</tbody>
</table>

*No significant differences by GNB3 genotype

mcnamara et al, JACC-HF 2014
Impact of I/H on composite score in A-HeFT: GNB3 TT genotype subset versus C allele (TC+CC)

*\(p=0.016, n=184\)

\(p=0.871, n=166\)

mcnamara et al, JACC-HF 2014
Impact of I/H on Quality of Life (QoL) Score: GNB3 TT genotype versus C allele (TC+CC)

- GNB3 TT only: *p=0.039, n=184
- GNB3 TC+CC: p=0.563, n=166

Source: mcnamara et al, JACC-HF 2014
Impact of I/H on Event Free Survival: GNB3 TT versus C haplotype

$p=0.047$

mcnamara et al, JACC-HF 2014
**Results:** The proportion of European ancestry in the cohort is $15.6 \pm 8.4\%$, with the detailed histogram of proportions of European ancestry given in Figure 1 below.

![Histogram of European ancestry proportions](image)

**Figure 1:** Proportions of European ancestry in the 323 individuals from the A-HeFT study. The proportions are estimated by genotyping 1,287 ancestry-informative markers. Individual ancestry estimates are accurate to approximately $\pm 2.5\%$.

**Admixture analysis:** can be used for a genomic screen of a trait that is ‘Linked” to an ancestral genomic background (eg. hypertension and African genomic heritage)
IMAC2: Myocardial Recovery in Recent Onset Cardiomyopathy LVEF at entry and 6 months by race

McNamara et al, JACC, 2011
IMAC2: Survival Free from HF Hospitalization: Blacks (n=80) versus whites (n=293)

Events=62

% 1/2/3 years
whites = 90/86/84
Blacks= 83/69/64

$p=0.001$

McNamara et al
JACC, 2011
IMAC therapy by Race: Time to ICD/BiV (events 109)

% on Medical Therapy: ACEi/Beta Blockers

Whites = 83%/80%

Blacks = 80%/87%

p = 0.97
IMAC II  HF Hospitalization free Survival by GNB3 Genotype (n= 360)

$p=0.486$

$p=0.486$

$p=0.05$
GNB3 and Transplant free survival: GRACE2 (n=460)

\[ p = 0.003 \]
PPCM (IPAC): Recovery of LVEF: blacks versus whites

<table>
<thead>
<tr>
<th>Time</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.28</td>
<td>0.36</td>
</tr>
<tr>
<td>6 months</td>
<td>0.47</td>
<td>0.53</td>
</tr>
<tr>
<td>12 months</td>
<td>0.47</td>
<td>0.55</td>
</tr>
</tbody>
</table>

- p-value at baseline: 0.002 (63/28)
- p-value at 6 months: 0.02 (46/19)
- p-value at 12 months: 0.02 (31/10)
LVEF by GNB3: IPAC (all)
TT versus CC+TC

LVEF (%)

baseline
6 month
12 month

GNB3 TT
GNB3 TC+CC

p=0.054
P=0.002
P=0.0001

N=22
N=19
N=17
N=75
N=58
N=57
N=97
N=77
N=71

N=58
N=56

LVEF (%) by GNB3: IPAC (all)
TT versus CC+TC

p=0.054
N=97

P=0.002
N=77

P=0.0001
N=71
LVEF by GNB3: IPAC (black)
TT versus CC+TC

- **Baseline**: GNB3 TT (N=15), GNB3 TC+CC (N=14)
  - GNB3 TT: 28%
  - GNB3 TC+CC: 35%
  - p-value: 0.04

- **6 Month**: GNB3 TT (N=12), GNB3 TC+CC (N=11)
  - GNB3 TT: 41%
  - GNB3 TC+CC: 52%
  - p-value: 0.08

- **12 Month**: GNB3 TT (N=10), GNB3 TC+CC (N=12)
  - GNB3 TT: 37%
  - GNB3 TC+CC: 53%
  - p-value: 0.02
Confirmation of the impact of \textit{GNB3 GRAHf (AHeFT)}

- Would identify 50\% of African American Cohort with enhanced benefit from FDC I/H

- Impact on “Ordering” of therapy in African Americans

- Potential marker of benefit in non-African American cohorts
GRAHF

Genetic Risk Assessment in Heart Failure

GRAHF2

Genomic Response Analysis of Enhanced Heart Failure Therapy in African Americans
Open label treatment with fixed dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in a cohort of 500 self designated African Americans with systolic heart failure and AHeFT entry criteria at 15 centers

DNA for genotyping and serum assessment of biomarkers at baseline

Followed for up to 2 years on therapy
Primary Hypothesis: The GNB3 TT genotype will identify subjects with the greatest clinical benefit from treatment with FDC I/H

Comparison

- Composite Score of GNB3 TT subjects compared to subjects with the C allele (GNB3 CC plus TC)
GRAHF: Only subjects on FDC I/H, Composite Score

\[ p=0.03, \ n=164 \]
GRAHF2: Genomics

- Replicate the GRAHF SNP “Panel”
  - GNB3, NOS, Beta receptors, Aldosterone synthase, ACE D/I

- Perform admixture analysis
  - Determine % African Genomic Heritage for each subject and analyze as a “modifier” of therapeutic impact of FDC I/H.
  - Search for genomic loci responsible for impact by admixture analysis
GRAHF2: Time Line

- Enrollment to be initiated nationally this spring
- Enrollment of 500 subjects at 10-15 sites through 2016
- Complete 2 year follow up in 2018
Targeting Therapeutics: ACEi and ISDN-HYD

ISDN-HYD
- GNB3 TT
- NOS3 Glu-Glu

ACE inhibitors
- GNB3 CC
- NOS3 Asp

10% of whites, 50% of blacks

45% of whites, 15% of blacks
Genomic “Drivers”
ACEi and I/H

ACE inhibitor:
- GNB3 CC
- ACE DD
- Beta 1 Arg389Arg
- NOS3 Asp298

ISDN-HYD
- GNB3 TT
- NOS3 Glu298Glu
- Ald. Syth -344 TT
Predictions... whether favorable or unfavorable, are not absolutely certain. The Aphorisms of Hippocrates

- Clinical decisions are based on probabilities
- Guidelines based practice treats populations
- Genomic targeting will treat individuals
- By optimizing individual impact, genomics can reduce disparities
Future Case Presentation

- 50 year old man with heart failure present for optimization of medical therapy. NYHA class 2 limitations.

- On genotyping: GNB3 TT, ACE II, $\beta_1$ Arg389Arg, NOS3 Glu298Glu, Aldosterone synthase -344TC, alpha 2c deletion/insertion

- ACEi allele score of 3/10 (minimal to no benefit) an I/H allele score of 5/6 (maximal benefit), and a beta blocker score of 3/6 (intermediate benefit)

- Treatment with I/H as first line agent, and beta blockers as second line is recommended. ACEi not felt to be beneficial.