Should Genetics Influence Medication Use?

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Population Differences

- Genetic information of humans is 95-99% identical

- The differences in genomes make us unique
  - Eye, hair and skin color
  - Sensitivity to sunlight
  - Predisposition to disease
  - Response to drugs

Adapted from Nature Genetics 2007
Pharmacogenetics

– Explores the way genetic differences can be used to predict how a patient responds to a drug:

  » Efficacy
  » Toxicity
  » Discovery/Development
Pharmacogenetics in Practice: Oncology

- **HER2/neu gene (breast ca)** — treatment with Herceptin (trastuzumab) is only effective in breast cancer where the HER2/neu receptor is overexpressed.

- **BCR-ABL fusion gene (CML)** — tyrosine kinase (TK) inhibitors such as Gleevec (imatinib) target dysregulated TK receptors.

- **UGT1A1 gene (colon ca)** — identifies patients predisposed to severe neutropenia on Camptosar (irinotecan).

- **TPMT gene (leukemia)** — identifies patients who have slower metabolism and are predisposed to fatal neutropenia with thiopurines.
Pharmacogenetics in Practice: Warfarin

- Cyp2C9
  - Metabolism
  - 2C9 *1 vs. *2 or *3

- VKORC1
  - Sensitivity
  - AA/AG/GG
**Clopidogrel: Pharmacogenomics - CYP2C19**

*17 = Gain-of-Function SNP  
(~34% Caucasians, 30% African Americans, 4% Asians)

*2, *3 = Loss-of-Function SNP  
(~25% Caucasians, ~33% African Americans, ~55% Asians)

*1 = Wild type

**Common CYP2C19 Genotypes**

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>*17/*17, *17/*1</td>
<td>Extensive Metabolizer (EM)</td>
</tr>
<tr>
<td>*1/*1, *17/*2</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>*1/*2</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>*2/*2</td>
<td>Poor Metabolizer (PM)</td>
</tr>
</tbody>
</table>

- Extensive Metabolizer (EM): 34% Caucasians, 30% African Americans, 4% Asians
- Normal Metabolizer (NM): 24% Caucasians, 30% African Americans, 46% Asians
- Intermediate Metabolizer (IM): 2% Caucasians, 3.5% African Americans, 10% Asians
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].

How many of our patients have a decreased function CYP2C19?

Caucasian (15%), African-Am (17%), Asian (30%)
Polymorphisms in Large HF Trials

- AHeFT (GRAHF) – aldosterone synthase promoter polymorphisms
- CHARM – angiotensin II type 1 receptor polymorphisms
- MERIT-HF, BEST – beta adrenergic receptor polymorphisms
- BEST – alpha adrenergic receptor polymorphisms
BEST

• 1995 – 1999: Beta Blocker Evaluation of Survival Trial ("BEST") was an n = 2708 survival trial in advanced heart failure patients, Bucindolol was the beta blocker selected for this VA/NHLBI sponsored trial.

• In 1999, the BEST Trial was stopped early by the DSMB due to historical events occurring at this time: results of other BB trials (MERIT-HF and Copernicus) and loss of investigator equipoise

• BEST contained an n = 1040 DNA substudy

• BEST DNA substudy was a prospectively designed protocol which tested the hypothesis that important polymorphisms would interact with bucindolol’s treatment effects
β₁-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure

Jeanne Mialet Perez¹,4, Deborah A Rathz²,4, Natalia N Petrashevskaya³, Harvey S Hahn¹, Lynne E Wagoner¹, Arnold Schwartz³, Gerald W Dorn II¹,² & Stephen B Liggett¹,²

Catecholamines stimulate cardiac contractility through β₁-adrenergic receptors (β₁-ARs), which in humans are polymorphic at amino acid residue 389 (Arg/Gly). We used cardiac-targeted transgenesis in a mouse model to delineate mechanisms accounting for the association of Arg389 with human heart failure phenotypes. Hearts from young Arg389 mice had enhanced receptor function and contractility compared with Gly389 hearts. Older Arg389 mice displayed a phenotypic switch, with decreased β-agonist signaling to adenylyl cyclase and decreased cardiac contractility compared with Gly 389 hearts. Arg389 hearts had abnormal expression of fetal and hypertrophy genes and calcium-cycling proteins, decreased adenylyl cyclase and Gx₅₄ expression, and fibrosis with heart failure. This phenotype was recapitulated in homozygous, end-stage, failing human hearts. In addition, hemodynamic responses to β-receptor blockade were greater in Arg389 mice, and homozygosity for Arg389 was associated with improvement in ventricular function during carvedilol treatment in heart failure patients. Thus, the human Arg389 variant predisposes to heart failure by instigating hyperactive signaling programs leading to depressed receptor coupling and ventricular dysfunction, and influences the therapeutic response to β-receptor blockade.

β-1 Adrenergic Receptor Arg389Gly Polymorphism

Taylor M, Bristow MR, Cong Heart Failure 10:281-288, 2004
BEST trial, *all-cause mortality* (covariate adjusted)

![Graph showing survival probability over months after randomization.](image)

- **Placebo**
- **Bucindolol**

HR = 0.87 (0.76, 1.00)

841 Ev, p = 0.053

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BEST: Hazard ratios for 1st clinical events by $\beta_1$AR 389 genotype

<table>
<thead>
<tr>
<th>Survival &amp; CHF Hospitalization</th>
<th>Bucindolol Better</th>
<th>Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gly Carrier</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg</td>
<td></td>
<td></td>
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<tr>
<td><strong>CHF Hospitalization</strong></td>
<td></td>
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<tr>
<td><strong>Gly Carrier</strong></td>
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<tr>
<td>Arg/Arg</td>
<td></td>
<td></td>
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<tr>
<td><strong>CV Hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gly Carrier</strong></td>
<td></td>
<td></td>
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<tr>
<td>Arg/Arg</td>
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</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gly Carrier</strong></td>
<td></td>
<td></td>
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<tr>
<td>Arg/Arg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Liggett et al. PNAS 103:11288-11293, 2006
β₁AR 389 genotype

- Allele freq (BEST) Arg homozygotes = 57% in blacks, 72% in non-blacks (p <0.01)
  - Arg homozygous at a.a. 389 of the b1-AR increases efficacy of b-AR agonists by 3-4 fold
  - Bucindolol mortality reduction is 3.8 fold >than in Gly carriers
An α2C-Adrenergic Receptor Polymorphism Alters the Norepinephrine Lowering Effects and Therapeutic Response of the Beta Blocker Bucindolol in Chronic Heart Failure


CIRCULATIONAHA/2009/885962 [R1]
# Combinatorial Pharmacogenetic Interactions of Bucindolol and $\beta_1$, $\alpha_2c$ Adrenergic Receptor Polymorphisms


## Table

<table>
<thead>
<tr>
<th></th>
<th>Total BEST Cohort</th>
<th>$\beta_1$389 Arg/Arg + $\alpha_2c$-Wt/Wt or Del</th>
<th>$\beta_1$389 Gly carrier + $\alpha_2c$-Wt/Wt</th>
<th>$\beta_1$389 Gly carrier + $\alpha_2c$-Del322-325</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2708</td>
<td>N=493</td>
<td>N=413</td>
<td>N=134</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.87$^a$ (0.76, 1)</td>
<td>0.62$^b$ (0.39, 0.99)</td>
<td>0.75 (0.48, 1.17)</td>
<td>1.04 (0.43, 2.54)</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>0.84$^b$ (0.72, 0.97)</td>
<td>0.52$^b$ (0.31, 0.88)</td>
<td>0.6$^b$ (0.36, 0.97)</td>
<td>1.11 (0.45, 2.78)</td>
</tr>
<tr>
<td>HF hosp.</td>
<td>0.76$^c$ (0.66, 0.87)</td>
<td>0.56$^d$ (0.39, 0.82)</td>
<td>0.77 (0.53, 1.13)</td>
<td>0.73 (0.35, 1.53)</td>
</tr>
<tr>
<td>CV hosp.</td>
<td>0.82$^c$ (0.73, 0.91)</td>
<td>0.64$^d$ (0.48, 0.86)</td>
<td>0.91 (0.68, 1.22)</td>
<td>0.96 (0.53, 1.76)</td>
</tr>
</tbody>
</table>

$^a P=0.053$; $^b P<0.05$; $^c P<0.001$; $^d P<0.01$; HR and 95% CI adjusted for gender, race, CAD, and LVEF
What is the prevalence of these genotypes?

**Table 2:** Allele Frequencies of α2-, β1- and β2AR Polymorphisms in Caucasians and African-Americans

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Caucasians</th>
<th>African-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2C</td>
<td>Del322-325</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>β1</td>
<td>Arg-389</td>
<td>0.73</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Anti-arrhythmic effects of bucindolol in BEST PGx, by genotype from BEST AE database

Ev/n: placebo bucindolol

AF

VT/VF

Crude Effect Size, %

- V Favorable
- Favorable
- Unfavorable

p = 0.73
p = 0.95
p = 0.085
p = 0.86
p = 0.032
p < 0.0001
p = 0.0001
p = 0.006
p = 0.006
p = 0.032
p = 0.006
p = 0.032
Phase 2b Superiority Trial Design
Bucindolol vs. Metoprolol CR/XL, Prevention of Recurrent Atrial Fibrillation in Persistent AF HFREF Patients with the β₁389 Arg/Arg Genotype post Electrical Cardioversion (ECV), + Adaptive Design to Phase 3

LVEF <0.50, Class II-III HF w/in 90 days
No contra-indications to β-blockers
β₁389 Arg/Arg genotype

Sample size estimates

<table>
<thead>
<tr>
<th>n</th>
<th>Effect size</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α = 0.10</td>
<td>α = 0.05</td>
</tr>
<tr>
<td>200</td>
<td>25%</td>
<td>84</td>
</tr>
<tr>
<td>620</td>
<td>25%</td>
<td>–</td>
</tr>
</tbody>
</table>

Event rate M group 60%, ITT from time of randomization

Recent onset Sx AF, 1 wk – 90 d Class I-III HF

Time 0 (conversion to AF counted as if ECV)

Projected:
Trial Initiation – 2H 2013
Trial Data – 1H 2016

AF free/event: from 24 hrs after ECV

1° Endpoint = recurrent AF or ACM, 24 weeks; 2° EP = AF burden

**Note:** (FDA has indicated it would approve an AF indication on the basis of a single trial with this design, with an outcome of \( p \leq 0.010 \); adaptive scale up to \( n = 620 \) possible)
• Drug responses

• Dose responses
Patients with ACE DD genotype - benefit on BB

**Figure 4.** Transplant-free survival compared by β-blocker use for patients with *ACE DD* genotype only, n=105. Event-free survival was significantly better for patients treated with β-blockers (n=43) compared with those not receiving therapy (n=62) (P=0.007 by log-rank test).

McNamara D. Circulation. 2001;103:1644-1648
ACE Genotype - II homozygotes need higher dose of ACE inhibitor for similar benefit.

Figure 2. (A) Transplant-free survival by angiotensin-converting enzyme (ACE) genotype: low-dose ACE inhibitor (n = 227, p = 0.032). (B) Transplant-free survival by ACE genotype: high-dose ACE inhibitor (n = 201, p = 0.64).

Association between adrenergic receptor genotypes and beta-blocker dose in heart failure patients: analysis from the HF-ACTION DNA substudy

Mona Fiuzat\textsuperscript{1*}, Megan L. Neely\textsuperscript{1}, Aijing Z. Starr\textsuperscript{1}, William E. Kraus\textsuperscript{1}, G. Michael Felker\textsuperscript{1}, Mark Donahue\textsuperscript{1}, Kirkwood Adams\textsuperscript{2}, Ileana L. Piña\textsuperscript{3}, David Whellan\textsuperscript{4}, and Christopher M. O’Connor\textsuperscript{1}

\textsuperscript{1}Duke University and the Duke Clinical Research Institute, Durham, NC, USA; \textsuperscript{2}University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; \textsuperscript{3}Montefiore Einstein Center for Heart and Vascular Care, Bronx, NY, USA; and \textsuperscript{4}Thomas Jefferson University, Philadelphia, PA, USA
HF-ACTION

- 2331 patient randomized control trial of exercise training in patients with heart failure (NYHA Class II-IV, LVEF $\leq 0.35$, median follow-up 2.5 years).
- Sponsored by NIH/NHLBI
- Randomized to exercise training or usual care
- Primary endpoint of all-cause mortality + all-cause hosp.
- DNA Substudy (n=957)
Objectives

• We aimed to examine whether genetic variations in the β1-389 arginine (Arg)/glycine (Gly) adrenergic receptor may have an interaction with the dose requirements of β-blockers in patients with systolic heart failure.

• Endpoints:
  – Primary EP: all-cause mortality + all-cause hospitalization,
  – Secondary endpoint: all-cause mortality.

• Relationship assessed using Cox proportional hazards regression model.
Results

• No interaction on EP of ACM + ACH
• β1-389 Arg/Arg on low-dose β-blockers had 2x increase in risk of death vs. high dose (HR=2.16; p=0.01),
• Not conferred in Gly carriers
• KCCQ score: higher doses of β-blockade needed to achieve benefit in Arg/Arg patients.
Summary of AR gene variant HF clinical studies

- Underpowering is a major problem (as for most other Gx studies)
  - trials should have a sample size of at least $n = 1000$
  - major clinical events should be $>100$

- General lack of prospective, placebo controlled studies

- Data thus far suggest no effect of $\beta$AR variants on HF risk or natural history; some evidence for a $\alpha_{2c}$ Del 322-325 effect that needs confirmation

- Data for interaction with $\beta$-blocker therapy is more encouraging, but effect may be drug-specific (bucindolol)
Conclusions

• There are challenges and opportunities in the field of PM
• Research is ongoing
• Cautious interpretation and rigorous testing
• There could be variation in response to drugs, particularly BB’s, which may be genetically mediated
Table 1. Polymorphisms and the possible association with heart failure therapy.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Possible association</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₁ AR (β₁389)</td>
<td>Arg389Gly</td>
<td>β-blockers</td>
</tr>
<tr>
<td>β₁ AR (β₁49)</td>
<td>Ser49Gly</td>
<td>Exercise</td>
</tr>
<tr>
<td>β₂ AR (β₂16)</td>
<td>Arg16Gly</td>
<td>Exercise</td>
</tr>
<tr>
<td>β₂ AR (β₂27)</td>
<td>Gln27Gly</td>
<td>Exercise</td>
</tr>
<tr>
<td>α₂c AR</td>
<td>α₂c 322–325 del</td>
<td>β-blockers</td>
</tr>
<tr>
<td>CYP11B2</td>
<td>C-344T</td>
<td>Aldosterone receptor antagonists</td>
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<tr>
<td></td>
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<td>ISDN/hydralazine</td>
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<td>GNB3</td>
<td>C825T</td>
<td>ACE-inhibitors</td>
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<td>ACE I/D</td>
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<td>AGTR1</td>
<td>A1166C</td>
<td>ARBs</td>
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<td>NOS3</td>
<td>Asp298Glu</td>
<td>ACE-inhibitors</td>
</tr>
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<td></td>
<td></td>
<td>ISDN/hydralazine</td>
</tr>
</tbody>
</table>

Fiuzat et al. Personalized Medicine; July 2009. 6(4):385-392
Duke CV Genetics / PGx clinic

• Purpose: evaluation for patients who have (or are at high risk) for ADR’s to a CV Rx.
• Multi-disciplinary team approach (cardiologist, pharmacology, and genetic counseling)
• Referrals for:
  – stent thrombosis on clopidogrel
  – myopathy on statins
  – bleeding on warfarin
  – bradycardia on metoprolol
• Pharmacogenetic testing and other novel methods (such as platelet function testing) as necessary, interpretation, and recommendations for the referring physician.
SURE WE CAN FIND THE CAUSE. I'LL JUST SCHEDULE ANOTHER MRI, CAT SCAN, ELECTROCARDIOGRAM, COLONOSCOPY, BLOOD TEST......
Thank You