Pharmacogenetics of Chronic Cardiovascular Drugs: Applications and Implications

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April 11, 2008

Acknowledgments and Disclosures

American Heart Association Florida/Puerto Rico Affiliate
American College of Clinical Pharmacy Frontiers Fund
National Institutes of Health

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Arca Discovery, Inc
42 North Consulting Group, LLC (www.42ncg.com)
1. Variability in CV drug responses exists
2. Pgx-enhanced treatment decisions
3. Antihypertensive Pgx
4. Statin Pgx
5. Future directions and translation to practice

### Variability in Cardiovascular Drug Response

#### Antihypertensives

<table>
<thead>
<tr>
<th>Systolic Blood Pressure</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLON</td>
<td>62</td>
</tr>
<tr>
<td>HCTZ</td>
<td>60</td>
</tr>
<tr>
<td>DILT</td>
<td>52</td>
</tr>
<tr>
<td>ATEN</td>
<td>51</td>
</tr>
<tr>
<td>PRAZ</td>
<td>43</td>
</tr>
<tr>
<td>CAPT</td>
<td>39</td>
</tr>
<tr>
<td>PLAC</td>
<td>30</td>
</tr>
</tbody>
</table>

#### Statins

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Lipid</th>
<th>CARE</th>
<th>HPS</th>
<th>WOS</th>
<th>AFCAPS/TexCAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low Risk</td>
<td>High Risk</td>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary</td>
<td>High Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>62%</td>
<td>75%</td>
<td>75%</td>
<td>73%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75%</td>
<td>75%</td>
<td>73%</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Warfarin

<table>
<thead>
<tr>
<th>Range</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-1.49</td>
<td>12.2</td>
</tr>
<tr>
<td>1.50-1.99</td>
<td>26.3</td>
</tr>
<tr>
<td>2.00-3.00</td>
<td>40.8</td>
</tr>
<tr>
<td>3.00-3.49</td>
<td>7.4</td>
</tr>
<tr>
<td>3.50-4.99</td>
<td>5.7</td>
</tr>
<tr>
<td>≥5.00</td>
<td>17.3</td>
</tr>
</tbody>
</table>

Materson et al. 1993 [PMID 11701642]

**ADRB1 Variation**

**Functional Effects in vitro**

- **Ser49→Gly**
  
  *Gly allele* → lower N-glycosylation and basal activity; greater agonist-mediated downregulation and agonist affinity

- **Arg389→Gly**
  
  *Gly allele* → reduced G_s coupling, lower basal and agonist-stimulated adenylyl cyclase activity

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**Beta-blocker BP Response Variability**

- Graph showing systolic blood pressure (% of patients) for different drugs:
  - CLON: 178
  - HCTZ: 188
  - DILT: 185
  - ATEN: 178
  - PRAZ: 188
  - CAPT: 188
  - PLAC: 187

P < 0.001
**ADRB1 Polymorphism and Response to Metoprolol**

Johnson et al. 2003 [PMID 12844134]

Response to Metoprolol by $\beta_1$AR Diploptype

Johnson et al. 2003 [PMID 12844134]
### CYP2D6 Polymorphisms and Adverse Events

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Parameter Estimate</th>
<th>Partial R²%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline daytime DBP</td>
<td>0.79</td>
<td>35.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arg389Arg genotype</td>
<td>-8.33</td>
<td>15.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Ser49Ser genotype</td>
<td>-5.05</td>
<td>4.6</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Expected DBP (mm Hg) = 18.82 + 0.79(baseline daytime DBP) – 8.3(if Arg389Arg) – 5.1(if Ser49Ser)**

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### Factors Influencing Response in Multivariate Analysis

<table>
<thead>
<tr>
<th>S-metoprolol AUC quartile</th>
<th>General adverse event rate (%)</th>
<th>Dose-limiting adverse event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 12) (0.48-3.33)</td>
<td>66.7 (35.4-88.7)</td>
<td>16.7 (2.9-49.1)</td>
</tr>
<tr>
<td>2 (n = 13) (3.53-5.90)</td>
<td>53.8 (26.1-79.6)</td>
<td>23.1 (6.2-54.0)</td>
</tr>
<tr>
<td>3 (n = 13) (6.07-8.72)</td>
<td>23.1 (6.2-54.0)</td>
<td>7.7 (0.4-37.9)</td>
</tr>
<tr>
<td>4 (n = 12) (8.92-23.05)</td>
<td>41.7 (16.5-71.4)</td>
<td>8.3 (0.4-40.2)</td>
</tr>
</tbody>
</table>

**CYP2D6 activity score quartile**

| 1 (lowest) (n = 15)                       | 46.7 (22.3-72.6)                | 13.3 (2.3-41.6)                     |
| 2 (n = 11)                               | 63.6 (31.6-87.6)                | 18.2 (3.2-52.2)                     |
| 3 (n = 11)                               | 36.4 (12.4-68.4)                | 27.3 (7.3-60.7)                     |
| 4 (highest) (n = 13)                     | 38.5 (14.1-67.7)                | 0 (0-28.3)                          |

**P value**

- 0.09
- 0.35
- 0.45
- 0.47

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Zineh et al. 2004 [PMID 15592325]

Johnson et al. 2003 [PMID 12844134]
Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)

PEAR: Overview of Study Design

Eligibility determination and baseline studies → Randomization

HCTZ 12.5 mg → HCTZ 25 mg → HBP and ABP response assessment + labs → Add atenolol 50 mg → Atenolol 100 mg → Final HBP and APB response assessment + labs

Atenolol 50 mg → Atenolol 100 mg → HBP and ABP response assessment + labs → Add HCTZ 12.5 mg → HCTZ 25 mg → Final HBP and APB response assessment + labs

Study entry

2-6 weeks, depending on treatment at entry

Randomization

approx 6-9 weeks

Response assessment #1

Response assessment #2

Indicates action in patients with BP at goal

Indicates normal progression through study protocol
Outline

1. Variability in CV drug responses exists
2. Pgx-enhanced treatment decisions
3. Antihypertensive Pgx
4. Statin Pgx
5. Future directions and translation to practice
Variability in Statin Responses – Lipids and CRP

Ridker et al. 2005 [PMID 15635109]

Statin Pharmacokinetics and Dynamics

Pharmacokinetics

Pharmacodynamics

www.pharmgkb.org
**CXCL5: A Statin Pharmacogenetic Candidate**

Constitutive Endothelial ENA-78 Production

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pEPA</th>
<th>pg/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Atorva 1</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Atorva 5</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Atorva 10</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Atorva 50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>


**INFORM: CXCL5 and 3-yr Mortality Post-ACS**

A. Overall Population

- G/G
- G/C
- C/C

P=0.002

B. Caucasians Only

- G/G
- G/C
- C/C

P=0.013

Age=61±12 yrs; White=79%; Women=36%; UA/NSTE/STE=40/31/29%
Statin Benefit Differs by CXCL5 Genotype

![Graph showing 3-yr Mortality Rate by CXCL5 Genotype and Statin Treatment]

- G/G: 158% reduced mortality
- G/C: 125% reduced mortality
- C/C: 39% increased mortality

*P = 0.0009

Atorvastatin Modulates Endothelial CXCL5 During Inflammation

![Graph showing ENA-78 changes with different treatments and time]

- Dose-Dependent
- Time-Dependent

- ENA-78 Relative Changes over Time (hours)
1. Variability in CV drug responses exists
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Prospective Genotype-Stratified CGS

Zineh I. 2007 [PMID 18241612]
Pharmacogenetics of Statin Exposure and Response (POSTER)

Anti-inflammatory Effects

Drug Concentrations

www.pharmgkb.org | Lamba et al. 2002 [PMID 12406645]

WBC Gene Expression in Response to HD-Atorva (1)

CYP3A5 - (*3/*3)

CYP3A5 + (*1/*3)

Gene

CYP3A5 - (*3/*3)

CYP3A5 + (*1/*3)

Gene

Fold change

-15  -10  -5   0    5    10   15

Fold change

-20   -10   0    10   20   30   40   50   60   70
WBC Gene Expression in Response to HD-Atorva (2)

Gene

- APOE
- FN1
- HREG
- HPRT1
- IL1A
- IL5
- LPL
- SELE
- SPP1
- TNC
- VWF

Fold change

CYP3A5 +
CYP3A5 -

Atorva Lactone Concentrations by CYP3A5 Genotype

Skotthen et al. 2008 [PMID 18294823] | Hermann et al. 2006 [PMID 16765141]
Integrative Approach to Pharmacogenetics

- canSNP
- tSNP
- pfSNP
- Linkage
- WGA

Informatics

Putative causal SNP/haplotype

Public curated database

Replication studies

In silico

In vitro

Evidence Base For Translation Into Practice

- Polymorphisms of interest, identified through candidate gene or genome wide association studies
- Clinical associations documented
- Functional basis of genetic associations defined
- Genetic information sufficiently explains response variability to be useful clinically (usually multiple genes)
- Document pharmacogenetic superiority: Pharmacogenetic-guided versus usual care

IWPC

Acknowledgments

**Zineh Lab**
- Gregory Welder
- Amy DeBella
- Elvin Price
- Julio Duarte

**University of Florida**
- Amber Beitelshees, PharmD, MPH
- Mike Pacanowski, PharmD
- Nasser Chegini, PhD
- Reginald Frye, PharmD, PhD
- Jonathan Shuster, PhD
- Doug Theriaque, MS

**Mid America Heart Institute**
- John Spertus, MD

**University of Colorado**
- Christina Aquilante, PharmD

**Physician Collaborators**
- Richard Schofield, MD
- Christopher Arant, MD
- Timothy Wessel, MD
- Michael Haller, MD

**Our Research Participants**