Pharmacogenomics for Cardiovascular Care

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State of the evidence in cardiovascular pharmacogenomics

- **Warfarin**
  - Steady-state dose
  - Bleeding risk

- **Clopidogrel**
  - Plasma concentration
  - Platelet activity
  - Clinical outcomes

- **Statins**
  - Muscle toxicity
  - LDLc response

- **Aspirin**
  - Resistance to treatment

- **β-blockers**
  - Treatment response

- **ACEi and thiazides**
  - Treatment response
  - Angioedema

- **Arrhythmia**
  - Drug-induced arrhythmia

Where pharmacogenomics matters

Single pathway to bioactivation: High-risk pharmacokinetics

- encainide
- clopidogrel
- tamoxifin
- codeine
Variable Response to Clopidogrel

“Resistance” = 31%

24 Hours After 300mg Clopidogrel
N=96, Elective PCI

Patients (%)

\[ \Delta \text{ Platelet Aggregation Before and After Clopidogrel (\%)} \]

“Resistance” = ≤10% Δ platelet aggregation

Gurbel PA et al., Circulation 2003;107:2908-2913
Clopidogrel pharmacokinetic and pharmacodynamic pathways
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotypes</th>
<th>Diplototype examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>One or more gain of function alleles</td>
<td>*17/*17, *1/*17</td>
</tr>
<tr>
<td>(~5-30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>two copies of functional alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>(~35-50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>one reduced and one nonfunctional allele</td>
<td>*1/*2, *1/*3</td>
</tr>
<tr>
<td>(~18-45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>no functional alleles</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
<tr>
<td>(~2-15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CPIC: Clinical recommendations for CYP2C19 and clopidogrel

- CPIC recommendations if genotype is already available
- ACC/AHA recommend case by case genotyping
- Not supported by RCTs

Emerging Data: CYP2C19 and outcomes with clopidogrel

Adjusted Hazard Ratio
LOF-CLOP vs LOF ALT: 2.21 (1.13-4.33) p=0.021
LOF-ALT vs non-LOF: 0.81 (0.48-1.35) p=0.41
Clinical implementation

Clopidogrel Poor Metabolizer Rules

Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-platelet response to clopidogrel (Plavix) therapy.

This patient has been tested for CYP2C19 variants, and the presence of the *2/*2 genotype has identified this patient as a Poor metabolizer of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

**Treatment modification is recommended if not contraindicated:**
- Prescribe prasugrel (EFFIENT) 10 mg daily and stop clopidogrel (PLAVIX), start date 10 AM

**Due to increased risk of bleeding compared to clopidogrel, prasugrel should not be given to patients:**
- that have a history of stroke or transient ischemic attack
- that are greater than 75 years of age
- whose body weight is less than 50 kg

(Caution patient's age: 75 years)
(Caution patient's weight: 50 kg)

Click here for more information

If prasugrel (EFFIENT) not selected, please choose desired action:
- Increase maintenance dose of clopidogrel (PLAVIX) 150 mg daily, start date 10AM
- Maintain requested daily dose of clopidogrel (PLAVIX) 75 mg daily, start date 10AM

**If not using prasugrel, please select a reason:**
- Contraindicated for prasugrel
- Potential side effects
- Patient costs for clopidogrel
- Other (Specify)

Click here for more information

**NOTE:** The Vanderbilt P&T Committee has recommended that prasugrel (if not contraindicated) should replace clopidogrel for Poor metabolizers; if this is not
Where pharmacogenomics matters

Off-target serious adverse effects

Drug

Off-target ADE (SJS, rashes, DILI, long QT)

• simvastatin
• carbamazepine
• clozapine
• haloperidol
• abacavir
• antibiotics
Simvastatin and muscle toxicity

• Statins have wide therapeutic index and severe ADRs relatively uncommon
• Most common statin-related ADR is skeletal muscle toxicity
  • Myalgias (pain) – 1-5% patients
  • Myopathy (pain with evidence of muscle degradation) – 1 in 1,000 patients
  • Rhabdomyolysis (severe muscle damage with acute kidney injury), 1 in 100,000 patients
• Risk factors: age, statin dose, concomitant fibrates
A case-control genome-wide association study (GWAS) investigating genetic variants associated with heart disease.

**Identify cases and controls**

**cases** (n=1,000) people with heart disease

**controls** (n=1,000) people without heart disease

**Genotype a million SNPs across the genome**

**Statistical analysis for SNPs association with case**

- **cases**: 62% C, 38% T
- **controls**: 49% C, 51% T

Image credit: Genome Research Limited
SLCO1B1 Variants and Statin-Induced Myopathy

- Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study.
- x axis is $-\log(p \text{ value})$ so a dot (representing a SNP) at 8 on the x axis has a p value of $p=1\times10^{-8}$ or $p=0.00000001$
Risk of myopathy associated with 80 mg daily simvastatin by \( SLCO1B1 \) rs4149056 genotype

Simvastatin metabolized primarily by CYP3A4 and transported into liver primarily by SLCO1B1 (OATP1B1).

Avoid 80 mg simvastatin in all patients (FDA)
  - Exception in patients taking this dose for over a year without signs/symptoms of muscle toxicity

SLCO1B1 genotyping may apply to other statins, but not currently sufficient evidence.

Simvastatin-induced muscle toxicity can still occur in absence of rs4149056

### Table 2: Dosing recommendations for simvastatin based on SLCO1B1 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for simvastatin</th>
<th>Dosing recommendations for simvastatin&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Classification of recommendations&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Normal myopathy risk</td>
<td>Prescribe desired starting dose&lt;sup&gt;b&lt;/sup&gt; and adjust doses of simvastatin based on disease-specific guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>Intermediate myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
<tr>
<td>Low function</td>
<td>High myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CK, creatine kinase.

<sup>a</sup>In all cases, the potential for drug–drug interaction should be evaluated before initiating a prescription. <sup>b</sup>The US Food and Drug Administration recommends against 80 mg (unless already tolerated for 12 months). <sup>c</sup>See the Supplementary Material online (text section titled "Levels of Evidence") for additional details regarding the three-tiered system used to grade the quality of evidence.
Where Pharmacogenomics Matters

Drugs with narrow therapeutic windows

- warfarin
- lithium
- digoxin
- some antibiotics (vancomycin)
Warfarin
Inter-individual variability in warfarin dose

- **SENSITIVITY**: VKORC1 -1639 A/A, CYP2C9 *3/*3
- **RESISTANCE**: VKORC1 -1639 G/G, CYP2C9 *1/*1

Frequency

Warfarin maintenance dose (mg/day)
## Warfarin package insert

### Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.
Multiple genes affecting warfarin dose

Hypoactive clotting factors II, VII, IX, X

Active clotting factors II, VII, IX, X

Vitamin KH₂

Vitamin K 2,3 epoxide

Hydroxy-vitamin K₁

Vitamin K₁

7-OH Warfarin
6-OH Warfarin

S-Warfarin

R-Warfarin

4-OH Warfarin

CYP4F2

NQO1

VKORC1

CYP2C9

CYP2C18
### Required Patient Information

<table>
<thead>
<tr>
<th>Field</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-Select-</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-Select-</td>
</tr>
<tr>
<td>Race</td>
<td>-Select-</td>
</tr>
<tr>
<td>Weight (lbs or kgs)</td>
<td></td>
</tr>
<tr>
<td>Height (feet and inches)</td>
<td></td>
</tr>
<tr>
<td>Smokes</td>
<td>-Select-</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>-Select-</td>
</tr>
<tr>
<td>Indication</td>
<td>-Select-</td>
</tr>
<tr>
<td>Baseline INR</td>
<td></td>
</tr>
<tr>
<td>Target INR</td>
<td></td>
</tr>
<tr>
<td>Amiodarone/Cordarone® Dose</td>
<td>mg/day</td>
</tr>
<tr>
<td>Statin/HMG CoA Reductase Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Any azole (eg. Fluconazole)</td>
<td>-Select-</td>
</tr>
<tr>
<td>Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim</td>
<td>-Select-</td>
</tr>
</tbody>
</table>

### Genetic Information

<table>
<thead>
<tr>
<th>Gene</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKORC1-1639/3673</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>CYP4F2 V433M</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>GGCX rs11676382</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>CYP2C9*2</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>CYP2C9*5</td>
<td>Not available/pending</td>
</tr>
<tr>
<td>CYP2C9*6</td>
<td>Not available/pending</td>
</tr>
</tbody>
</table>

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## Randomized controlled trials for warfarin pharmacogenomic testing

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Control group dosing algorithm</th>
<th>Clinical Factors included in algorithm(s)</th>
<th>Comparator Group (% TTR)</th>
<th>Genotype-Guided Group (% TTR)**</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirmohamed et al. 2013 (EU-PACT)</td>
<td>454</td>
<td>Fixed dose*</td>
<td>Age, Height, Weight, Amiodarone</td>
<td>60.3%</td>
<td>67.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kimmel et al. 2013 (COAG)</td>
<td>955 700 (non-AA), 255 (AA)</td>
<td>Clinically-derived dose</td>
<td>Age, Race, Smoking status, BSA, Amiodarone, Target INR,</td>
<td>45.4%</td>
<td>45.2%</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**46.1% (non-AA) 43.5% (AA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**48.8% (non-AA) 35.2% (AA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**0.15 (non-AA) 0.0003 (AA)</td>
<td></td>
</tr>
<tr>
<td>Verhoef et al. 2013 (EU-PACT)**</td>
<td>548</td>
<td>Clinically-derived dose</td>
<td>Age, Sex, Height, Weight, Amiodarone</td>
<td>60.2%</td>
<td>61.6%</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Fixed dose algorithm used no clinical factors and started with 10mg (day 1) and 5mg (days 2 and 3).

** All genotype-guided algorithms included clinical factors and genetic factors CYP2C9 *2,*3, and VKORC1 -1639A (or VKORC1 1173T).

***Study administered warfarin derivatives acenocoumarol and phenprocoumon.
Log-rank \( P = .04 \)

**Clinically guided dosing**

**Genotype-guided dosing**

- **No. of patients**
  - Clinically guided dosing: 789, 737, 698, 209
  - Genotype-guided dosing: 808, 771, 739, 216
CPIC: Clinical Recommendations (2017)

**VKORC1-1639G>A** and **CYP2C9*2** and **3** genotype available?

- **YES**
  - Self-identified ancestry
    - Non-African ancestry

- **NO**
  - Dose clinically<sup>a</sup>
  - **African ancestry**
    - **CYP2C9*5, *6, *8, and *11 also tested?**
      - **YES**
        - **1)** **VKORC1-1639G>A** and **CYP2C9*2** and **3**: Calculate dose based on validated published pharmacogenetic algorithms.
        - **2)** Carriers of **CYP2C9*5, *6, *8 or *11 variant alleles** (e.g., *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%<sup>g</sup>.

- **NO**
  - Carriers of **CYP2C9*5, *6, *8 or *11 variant alleles** (e.g., *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%<sup>g</sup>.

**OPTIONAL**

- Carriers of **CYP4F2 rs2108622 T allele**: Increase dose by 5-10%.

**MIXED-CASE**

**Health Sciences**

Genomics is failing on diversity

- Studies in whites may not be valid in other race/ethnic groups
- Without research, clinical testing may not be useful for non-whites

PERSISTENT BIAS
Over the past seven years, the proportion of participants in genome-wide association studies (GWAS) that are of Asian ancestry has increased. Groups of other ancestries continue to be very poorly represented.

2009
- 373 studies
- 1.7 million samples
  - 96% European ancestry
  - 4% Non-European ancestry

2016
- 2,511 studies
- 35 million samples
  - 81% European ancestry
  - 19% Non-European ancestry

BREAKDOWN
Proportion of non-European ancestry samples
- Asian ancestry
- African ancestry
- Mixed ancestry
- Hispanic & Latin American ancestry
- Pacific Islander
- Arab & Middle Eastern
- Native Peoples

Terms for ethnicity are those used in the GWAS Catalog. Some have changed between 2009 and 2015 as sampling has increased. Samples of European origin have the most specific descriptions of population ancestry.

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