Clinical Applications in Cardiovascular Pharmacogenetics

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Disclosure

• I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

• The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Objectives

- Describe clinical implications of genetic variability in cardiovascular pharmacotherapy.
- Discuss clinical, patient-specific, genetic, and other factors that inform drug therapy changes in cardiology.
- Summarize the structure and characteristics of representative cardiovascular pharmacogenetics implementations.
Clopidogrel Pharmacokinetics

Sangkuhl K et al. "Clopidogrel pathway" Pharmacogenet Genomics (2010). Copyright to PharmGKB.
# CYP2C19 Alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>Type of Variant</th>
<th>CYP2C19 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>N/A</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>Splicing defect</td>
<td>No function*</td>
</tr>
<tr>
<td>*3</td>
<td>Stop codon</td>
<td>No function</td>
</tr>
<tr>
<td>*4</td>
<td>Exon SNP</td>
<td>No function</td>
</tr>
<tr>
<td>*5</td>
<td>Exon SNP</td>
<td>No function</td>
</tr>
<tr>
<td>*6</td>
<td>Exon SNP</td>
<td>No function</td>
</tr>
<tr>
<td>*7</td>
<td>Splicing defect</td>
<td>No function</td>
</tr>
<tr>
<td>*8</td>
<td>Exon SNP</td>
<td>No function</td>
</tr>
<tr>
<td>*17</td>
<td>Increased expression</td>
<td>Increased function</td>
</tr>
</tbody>
</table>

*No function also referred to as loss-of-function*
### CYP2C19 Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>*1/*2, *1/*3, *2/*17</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>*2/*2, *2/*3</td>
<td>Poor Metabolizer (PM)</td>
</tr>
<tr>
<td>*1/*17</td>
<td>Rapid Metabolizer (RM)</td>
</tr>
<tr>
<td>*17/*17</td>
<td>Ultra-Rapid Metabolizer (UM)</td>
</tr>
</tbody>
</table>

*1 reported if other alleles measured are absent

Predicted metabolizer phenotype for *2-8/*17 considered provisional
Question

Based on your CYP2C19 genotype, what is your CYP2C19 phenotype?

1. Normal metabolizer
2. Intermediate metabolizer
3. Poor metabolizer
4. Rapid metabolizer
5. Ultra-rapid metabolizer
CYP2C19 Phenotype Prevalence

<table>
<thead>
<tr>
<th>Race</th>
<th>PMs</th>
<th>IMs</th>
<th>RM or UM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>2%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Blacks</td>
<td>4%</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Asian</td>
<td>14%</td>
<td>50%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
**CYP2C19** and Clopidogrel Response

- Nonfunctional alleles associated with:
  - Less active metabolite
  - Decreased antiplatelet effects
- Meta-analysis of 9 trials and 9685 patients treated with clopidogrel:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM vs NM</td>
</tr>
<tr>
<td>MACE*</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>2.7 (1.7-4.2)</td>
</tr>
</tbody>
</table>

*Major adverse CV events (CV death, MI, or stroke)

Other Meta-Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of studies</th>
<th>No. patients</th>
<th>HR or RR (95% CI) for LOF carriers vs NMs/UMs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CV events</td>
</tr>
<tr>
<td>Jang et al.</td>
<td>16</td>
<td>20,785</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Zabalza et al.</td>
<td>11</td>
<td>16,360</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>Holmes et al.</td>
<td>22</td>
<td>26,251</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Sorich et al.</td>
<td>17</td>
<td>26,059</td>
<td>Non-PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2 (1.1-1.3)</td>
</tr>
</tbody>
</table>

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
ACS/PCI Patients

CYP2C19 Genotyping

RM (*1/*17)
UM (*17/*17)

NM (*1/*1)

IM (e.g. *1/*2)

PM (e.g. *2/*2)

Clopidogrel at a standard dose

Alternative antiplatelet (Prasugrel or Ticagrelor)
Alternative $\text{P2Y}_{12}$ Inhibitors

Pharmacogenomics Pers Med 2011;4:123-36
Question

Based on your genotype results, would clopidogrel be expected to be effective for you?

1. Yes
2. No
6.1.2. Clopidogrel Genetic Testing: Recommendations

Class IIb
1. Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel.\textsuperscript{829} (Level of Evidence: C)

2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate P2Y\textsubscript{12} inhibitor (eg, prasugrel or ticagrelor) might be considered.\textsuperscript{829} (Level of Evidence: C)

Class III: NO BENEFIT
1. The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.\textsuperscript{829} (Level of Evidence: C)
TAILOR-PCI
ClinicalTrials.gov Identifier: NCT01742117

- TAILOR-PCI: Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Est. enrollment</th>
<th>5,270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>PCI</td>
</tr>
<tr>
<td>Arms</td>
<td>Genotype-guided strategy (Ticagrelor for CYP2C19*2 or *3 allele) versus clopidogrel</td>
</tr>
<tr>
<td>Outcomes</td>
<td>MACE at 1 year</td>
</tr>
<tr>
<td>Est. completion</td>
<td>3/2020</td>
</tr>
</tbody>
</table>
NIH IGNITE Pharmacogenetics Working Group

https://ignite-genomics.org/
Outcome Data from IGNITE PGx Working Group

• Prospective multi-center investigation of clinical CYP2C19 genotype-guided antiplatelet therapy post-PCI

• Primary outcome - Major Adverse Cardiac Events (MACE)
  – Death, myocardial infarction, or stroke within 12 months following index PCI
  – Compared between patients with a loss-of-function (LOF) allele on alternative vs. clopidogrel therapy
  – Also compared between patients with a LOF allele on alternative therapy vs. patients without a LOF allele
Outcome Data from IGNITE PGx Working Group

Total Cohort  
- n=1815

LOF  
- n=572 (31.5%)
  - Clopidogrel  
    - n=226 (39.5%)
  - Alternative  
    - n=346 (60.5%)*

non-LOF  
- n=1243 (68.5%)
  - Clopidogrel  
    - n=1050 (84.5%)
  - Alternative  
    - n=193 (15.5%)†

*p<0.0001 for Alternative therapy between LOF and non-LOF groups
Kaplan-Meier Survival Curve

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

Log-rank p=0.016
Log-rank p=0.15
Warfarin Dose Variability

**Warfarin Pharmacology**

- **CYP4F2** (Cytochrome P450 4F2) hydroxylates vitamin K$_1$.
- **Vitamin K$_1$** is converted to vitamin KH$_2$.
- **CYP2C9** metabolizes warfarin to 7-OH warfarin.
- **VKORC1**, vitamin K epoxide reductase complex subunit 1.
- **GGCX** converts vitamin KH$_2$ to hypofunctional clotting factors.
- **Functional clotting factors** (2, 7, 9, 10).
CYP2C9 Alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>SNP</th>
<th>Location</th>
<th>Whites</th>
<th>Blacks</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>p.Arg144Cys</td>
<td>Exon 3</td>
<td>20</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>*3</td>
<td>p.Ile359Leu</td>
<td>Exon 7</td>
<td>12</td>
<td>2</td>
<td>6-8</td>
</tr>
<tr>
<td>*5</td>
<td>p.Asp360Glu</td>
<td>Exon 7</td>
<td>ND</td>
<td>1-2</td>
<td>ND</td>
</tr>
<tr>
<td>*6</td>
<td>c.818delA</td>
<td>Exon 5</td>
<td>ND</td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>*8</td>
<td>p.Arg150His</td>
<td>Exon 3</td>
<td>ND</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>*11</td>
<td>p.Arg355Trp</td>
<td>Exon 7</td>
<td>ND</td>
<td>3-4</td>
<td>ND</td>
</tr>
</tbody>
</table>


CYP2C9 Genotype and Warfarin Dose Requirements in Caucasians

CYP2C9 Genotype and Warfarin Dose Requirements in African Americans

Clin Pharmacol Ther 2010;87:459-64
VKORC1 Genotype

- First described in the context of warfarin resistance due to rare mutations in the coding region (e.g. p.Asp36Tyr)
- More common polymorphisms occur in regulatory regions of the gene and are in strong linkage disequilibrium
  - c.-1639G>A SNP in promoter region
  - c.1173C>T SNP in intron 1
- -1639A allele associated with approximately 2-fold lower protein expression compared to the G allele
**VKORC1 -1639G>A Genotype**


<table>
<thead>
<tr>
<th>VKORC1 -1639G&gt;A</th>
<th>Sensitivity to warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>High</td>
</tr>
<tr>
<td>AG</td>
<td>Intermediate</td>
</tr>
<tr>
<td>GG</td>
<td>Low</td>
</tr>
</tbody>
</table>

Mean Warfarin Dose (mg/day)

**VKORC1 -1639 Genotype by Race**

- **Black**
  - GG
  - AG
  - AA

- **White**
  - GG
  - AG
  - AA

- **Asian**
  - GG
  - AG
  - AA
Warfarin Label Revision in 2007

Initial Dosage

The dosing of COUMADIN must be individualized according to patient’s sensitivity to the drug as indicated by the PT/INR….. It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations. The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients….”

### Warfarin Label Revision in 2010

- Maintenance dose requirements (mg/day) based on *CYP2C9* and *VKORC1* Genotypes

<table>
<thead>
<tr>
<th>VKORC1 -1639</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7</td>
</tr>
<tr>
<td>GA</td>
<td>5-7</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
</tr>
</tbody>
</table>
Factors Influencing Warfarin Dose Requirements

- Age
- Liver function
- Genotype
- Smoking
- Kidney function
- Body size
- Diet
- Concomitant therapy
- Concomitant therapy
Warfarin Pharmacogenetic Dosing Algorithms

• Gage et al.
  – *Clin Pharmacol Ther* 2008;84:326-31

• International Warfarin Pharmacogenetics Consortium (IWPC)
RCTs of Warfarin Pharmacogenetics


Genotypes limited to *VKORC1* -1639G>A and *CYP2C9*2 and *3
COAG Trial Results Continued

- African Americans

![Bar chart showing time in range at 30 days and percentage of time with INR > 3 for genotype and clinical groups.]

- Genotype (n=141)
- Clinical (n=134)

Statistical significance:
- p=0.01
- p=0.004
Limitations of RCTs

• Do not include many variants important in African Americans, which can lead to over-estimation of dose requirements

<table>
<thead>
<tr>
<th>Variant(s)</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12777823</td>
<td>&gt;40%</td>
<td>Lancet 2013;382(9894):790-6.</td>
</tr>
</tbody>
</table>

• No loading dose used in COAG
• Close INR monitoring, which may not be possible in clinical practice
• Primary endpoint was time within the therapeutic range
  – Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT examining clinical outcomes (ClinicalTrials.gov ID: NCT01006733)

Drozda et al. Pharmacogenet Genomics 2015;25(2):73-81
CPIC Guidelines for Warfarin
Johnson et al. *Clin Pharmacol Ther* 2017 (PMID 28198005)
Statin-Induced Myopathy

• Most common statin-related adverse drug reaction
• Symptoms range from mild myalgia to myopathy to rhabdomyolysis.
• Risk factors
  – Higher statin doses, older age, female sex, kidney dysfunction, hypothyroidism, intense physical activity
  – Use with drugs that increase statin bioavailability
  – Solute carrier organic anion transporting polypeptide 1B1 (SLCO1B1) genotype
SLCO1B1 and Statin-Induced Myopathy

- **SLCO1B1** gene encodes for the organic anion transporting polypeptide C (OATP1B1)
- OATP1B1 transports statins (except fluvastatin) to hepatocytes
- **SLCO1B1** c.521T>C (p.Val174Ala)
  - Reduces OATP1B1 transport function
  - Associated with decreased statin clearance and increased statin concentrations

SLC01B1 Effect on Statin Exposure

SEARCH Collaborative Study GWAS


- 85 cases with myopathy with simvastatin 80 mg/d and 90 controls
- c.521T>C variant identified as a risk factor for statin-induced myopathy
- Remained associated in replication cohort, with relative risk of 2.6 per C allele with the 40 mg/day dose.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>4.5 (2.6 to 7.7)</td>
</tr>
<tr>
<td>CC</td>
<td>16.9 (4.7 to 61.1)</td>
</tr>
</tbody>
</table>
Question

What is your SLCO1B1 genotype?

1. TT
2. TC
3. CC
## SLC01B1 Phenotype Prevalence


<table>
<thead>
<tr>
<th>rs4149056 Genotype</th>
<th>Phenotype</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>Normal function</td>
<td>55-88%</td>
</tr>
<tr>
<td>TC</td>
<td>Intermediate function</td>
<td>11-36%</td>
</tr>
<tr>
<td>CC</td>
<td>Low function</td>
<td>0-6%</td>
</tr>
</tbody>
</table>
## CPIC Guidelines for Simvastatin


<table>
<thead>
<tr>
<th>rs4149056 Genotype</th>
<th>Risk for Myopathy</th>
<th>Recommendation for Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>Normal</td>
<td>Dose based on disease-specific guidelines (Strong)</td>
</tr>
<tr>
<td>TC</td>
<td>Intermediate</td>
<td>Prescribe low dose or alternative statin; consider routine CK surveillance (Strong)</td>
</tr>
<tr>
<td>CC</td>
<td>High</td>
<td>Prescribe low dose or alternative statin; consider routine CK surveillance (Strong)</td>
</tr>
</tbody>
</table>
# Clinical Implementation

<table>
<thead>
<tr>
<th>Question</th>
<th>Clopidogrel</th>
<th>Simvastatin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent evidence that genotype influences drug response?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Genotype information in the drug labeling?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alternative drug/dosing available?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CPIC Guidelines?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reimbursed by payers?</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>