Cardiology PRN and American Heart Association Focus Session—The “Me” Generation of Healthcare: Personalized Medicine in Cardiovascular Disease
Activity No. 0217-0000-11-072-L01-P (Application-Based Activity)

Monday, October 17
1:30 p.m.–3:30 p.m.
Convention Center: Spirit of Pittsburgh Ballroom A

Moderators: Sheryl L. Chow, Pharm.D., BCPS (AQ Cardiology)
Assistant Professor, Western University of Health Sciences, Los Angeles, California

and

Robert L. Talbert, Pharm.D., FCCP, FAHA, BCPS
SmithKline Professor of Pharmacy, Division of Pharmacotherapy, The University of Texas at Austin; Professor of Medicine, The University of Texas Health Science Center, San Antonio, Texas

Agenda

1:30 p.m. What Is the Role of Warfarin Genotyping in Current and Future Clinical Practice?
Julie A. Johnson, Pharm.D., FCCP, FAHA, BCPS
V. Ravi Chandran Professor of Pharmaceutical Sciences, Distinguished Professor of Pharmacy; Departments of Pharmacotherapy and Translational Research (primary) and Pharmaceutics; and Professor of Medicine, Department of Medicine, Division of Cardiovascular Medicine at the University of Florida Colleges of Pharmacy and Medicine; Director, University of Florida Center for Pharmacogenomics and Director of the University of Florida and Shands Personalized Medicine Program, Gainesville, Florida

and

L. Kristin Newby, M.D., MHS, FAHA
Professor of Medicine and Cardiology, Duke University School of Medicine, Durham, North Carolina

2:30 p.m. Clopidogrel Pharmacogenomics: Will the FDA’s Black Box Change Practice?
Eric Bates, M.D., FAHA
Professor of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan

and

Craig R. Lee, Pharm.D., Ph.D.
Assistant Professor of Pharmacy, University of North Carolina at Chapel Hill, Eshelman School of Pharmacy, Chapel Hill, North Carolina
Faculty Conflict of Interest Disclosures

Eric Bates: consultant/member of advisory board for AstraZeneca, Eli Lilly, sanofi-aventis, Merck, Takeda
Julie A. Johnson: consultant/member of advisory board for Medco; clinical investigator for NIH; received grant funding from NIH.
Craig R. Lee: no conflicts to disclose.
L. Kristin Newby: received grant funding from Adolor Corporation; AstraZeneca, Biostie, Inc., Bristol Myers Squibb, Medicure, sanofi-aventis, Schering-Plough Corporation.

Learning Objectives

1. Identify the potential role of warfarin genotyping in current clinical practice.
2. Describe the benefits and limitations of warfarin genotyping.
3. Identify the potential role of clopidogrel genotyping in current clinical practice.
4. Describe the benefits and limitations of clopidogrel genotyping.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Warfarin pharmacogenetics has a role in current and future clinical practice

Julie A. Johnson, Pharm.D, BCPS, FCCP, FAHA
University of Florida
Gainesville, FL
Disclosure

- Site PI and Steering Committee Vice Chair for NHLBI COAG Trial
  - Genotype-guided warfarin trial
- Leader - International Warfarin Pharmacogenetics Consortium
- Advisory Board - Medco
Variability in drug response

WARFARIN

Liver function

Genetics

Disease phenotype

Body Size

Age

Environmental Factors (e.g. smoking)

Drug Response

Kidney function

Disease states

Other drugs

Foods

Figure 3. Trends in warfarin use and overall ischemic and hemorrhagic strokes among prevalent patients with AF.

*Lakshminarayan et al. Stroke 2006;37:1969*
Warfarin Pharmacogenetics

• 2 genes have proven consistently predictive and useful in prediction algorithms
  - CYP2C9
    • Alters metabolism of S-warfarin
      - Pharmacokinetic factor
  - VKORC1
    • Target of warfarin
      - Pharmacodynamic factor
Weekly dose by CYP2C9 genotype

CYP2C9 explains 5-15% of warfarin dose variability

International Warfarin Pharmacogenetics Consortium, NEJM 2009; 360: 760
Time to First Bleed

CYP2C9 variant carriers vs *1*1: HR 3.94

\[ \chi^2 = 6.21; P = .01 \]
VKORC1 genotype explains up to 30% of warfarin dose variability

International Warfarin Pharmacogenetics Consortium, NEJM 2009;360: 760
Coumadin label

FDA pharmacogenetics revisions to label: August 2007 and January 2010

Table 5: Range of Expected Therapeutic Warfarin 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. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.
How do you incorporate clinical AND genetic factors?

- www.warfarindosing.org
  - Algorithm developed by Brian Gage, Washington University; CPT 2008;84:326

- International Warfarin Pharmacogenetics Consortium
  - 21 research groups, 9 countries, 4 continents, n=5700; NEJM 2009; 360:760
Patient initiated on 5 mg/day with multiple high INRs.
Stable therapeutic dose was 2.14 mg/d (15 mg/wk)
Warfarin dose prediction: Clinical vs pharmacogenetics algorithms

International Warfarin Pharmacogenetics Consortium, NEJM 2009; 360: 760
Warfarin dosing precision by various approaches

[Graph showing the proportion within 20% of the therapeutic dose for different approaches: Empiric dose, Clinical algorithm, Warfarin label, Genotype mean table, Pharmacogenetic algorithm.]

JACC 2011;57:612 (PMID: 21272753)
Clinical validity proven: Genetic-guided dosing can improve warfarin dose prediction

- What are the arguments against its use in clinical practice?
  - No randomized controlled trials showing differences in outcomes
    - Also don’t have that for anticoag clinics
    - We do not ask for randomized controlled trials to show that using renal function to adjust dosing of drugs is better
      - why a different standard for genetics to guide dosing?
    - There is a prospective cohort study showing that patients with CYP2C9 and VKORC1 genotype had 30% in hospitalizations
Hospitalization rates in genotype group and historical controls
Arguments against use of warfarin pharmacogenetics

- Minimal evidence for improved time to stable INR, fewer OOR INRs
  - Multiple large randomized trials ongoing; US, Europe, Asia
- Can manage patient well through close monitoring of INR and dose adjustment
  - Not helpful for the 80+% of warfarin patients not managed in an anticoag clinic-type setting
    - PBM data - time to stable dose is about 90 days
    - Even in an excellent anticoag clinic, time to stable dose 95 days longer in CYP2C9 variant carriers (p=0.004). JAMA;2002;287:1690
Arguments against use of warfarin pharmacogenetics

- Have to order the test (hassle)
- Have to wait for the results (and INR data might reduce value of genotype)
  - Data suggest value of CYP2C9 genotype (even with INR) up to 10 days; perhaps 30 days
- Most insurance companies will not reimburse for the genetic testing ($$)
- Have to know what to do with the test result when it comes back (education)
- But..... What if none of these were issues?
Genomics, pharmacogenomics and the (near) future reality

- Human Genome Project finished ahead of 15 year planned duration; cost $2.7B (2001) - delivered 1 composite genome
- Today - personal genome costs $5,000 to $20,000, takes about 2 weeks
- In 2-3 years, expected to cost < $1000, take < 1 day
  - Discussions on replacing neonatal screening with whole genome sequencing
- At some point, the entire genome (or lots of genetic data) will be available for nearly all patients
Warfarin pharmacogenetic testing in the clinical setting: Now

- Given issues of cost (and unlikely reimbursement), and turn-around time, and lack of clear data on outcomes or time to stable INR
  - Reasonable to not use warfarin pharmacogenetic testing in broad population
    - Although 13M patients with Rx benefit through Medco have it available to them
  - May still have value in patient with unusual INR between days 4 and 10; may help clinicians move more quickly to the dose patient will actually require
Warfarin pharmacogenetics: The future

• If genetic data available
  - No delay - available immediately at time of warfarin prescription
  - Cost for genotyping already accrued
  - Smart EMR will incorporate genetic information and other factors to recommend warfarin dose

• Can one ignore the genetic information in selecting a starting warfarin dose if it were available?
  - Available data documents ability to better predict dose
Warfarin pharmacogenetics: The future

• **PREDICTION:** Genetic information will be routinely incorporated into the calculation of warfarin starting dose
Questions?
Genotyping for Antiplatelet Therapy

Two Perspectives: Con

Eric R. Bates, M.D.
Professor of Internal Medicine
University of Michigan
Conflicts of Interest

No conflicts to disclose.
Top 10 Reasons Why Genotyping for Antiplatelet Therapy Is Not Needed
Patient Compliance Is Much More Important

Overall ST=1.3% (P=0.09, n=2229)

CYP3A4 Activity/Conversion to Active Metabolite is Important

Clopidogrel-Drug Interactions May be Important

Clopidogrel Bisulfate

Intestinal Absorption 15%

Esterases 85%

Inactive Carboxylic Acid Metabolite

CYP3A4
CYP3A4/5 inducers: rifampin, St John's wort, etc.

CYP3A5
CYP3A4/5 inhibitors: erythromycin, atorvastatin, etc.

CYP2C19
2C19 inhibitors: omeprazole

CYP2C9
2C9 inhibitors: phenprocoumon

CYP1A2
Smoking (induction)

CYP2B6, 2C19

Multistep Conversion

Active Thiol Metabolite

P2Y₁₂ Receptor

Inhibition of Platelet Aggregation (Wide Response Variability)


There Are Other Genes

Intestinal Absorption

Poor compliance
Inadequate administration
Variable absorption

Hepatic Metabolism
Cytochrome P450 pathway

Genetic polymorphisms:
CYP2C19PMs, CYP2C9*3, ABCB1
Drug-drug interactions

Active Metabolite

Genetic polymorphisms:
P2Y12 receptor

P2Y12 Receptor (irreversible inhibition)

Genetic polymorphisms:
P2Y12 receptor

Alternate platelet activation pathways

GP IIb/IIIa receptor expression

Genetic polymorphisms

There are Other Platelet Receptors

- Thrombin
- ADP
- TBX A2
- Epinephrine
- Serotonin
- Collagen
- PAR-1
- PAR-4
- P2Y1
- P2Y12
- TBXA2-R
- GP IIb/IIIa
- GP Ia
- GP VI
- Fibrinogen
- GP IIb/IIIa
- Anionic phospholipid surfaces
There Are Important Clinical Factors
Not Much Contribution of CYP2C19*2 To Variation In Clopidogrel Responsiveness

Genome-wide Association Studies

Amish PAPI Study: 12%
EXCELSIOR Study: 11.5%

Loss-of-Function
Carrier Status Not Important in (Some) Clinical Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carrier Status</th>
<th>Placebo Event Rate</th>
<th>Clopidogrel Event Rate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Primary</td>
<td>Carriers</td>
<td>11.6% (78/674)</td>
<td>8.0% (52/651)</td>
<td>0.69 (0.49–0.98)</td>
</tr>
<tr>
<td></td>
<td>Noncarriers</td>
<td>13.0% (236/1819)</td>
<td>9.5% (179/1886)</td>
<td>0.72 (0.59–0.87)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>12.6% (314/2493)</td>
<td>9.1% (231/2537)</td>
<td>0.71 (0.60–0.84)</td>
</tr>
<tr>
<td>Second Primary</td>
<td>Carriers</td>
<td>19.0% (128/674)</td>
<td>15.7% (102/651)</td>
<td>0.81 (0.63–1.05)</td>
</tr>
<tr>
<td></td>
<td>Noncarriers</td>
<td>20.7% (376/1819)</td>
<td>16.8% (317/1886)</td>
<td>0.79 (0.68–0.92)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>20.2% (504/2493)</td>
<td>16.5% (419/2537)</td>
<td>0.79 (0.70–0.90)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>Carriers</td>
<td>2.2% (15/674)</td>
<td>3.2% (21/651)</td>
<td>1.50 (0.77–2.92)</td>
</tr>
<tr>
<td></td>
<td>Noncarriers</td>
<td>3.3% (60/1819)</td>
<td>4.3% (81/1886)</td>
<td>1.32 (0.94–1.84)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3.0% (75/2493)</td>
<td>4.0% (102/2537)</td>
<td>1.34 (1.00–1.81)</td>
</tr>
</tbody>
</table>

No heterogeneity for the first primary (P=0.84), second primary (P=0.87) or safety (P=0.74) endpoint

Phenotype Is More Important
On-Treatment Platelet Reactivity

PlateletWorks

Impedance Aggregometry (MULTIPLATE)

VerifyNow

PFA-100 ® analysis

Born aggregometry
There Are Better P2Y$_{12}$ Inhibitors

Clinical Outcomes: Carriers vs Non-carriers of a Reduced-function CYP2C19 Allele

- Prasugrel: 0.89, $P=0.27$
- Clopidogrel: 1.53, $P=0.01$

Top 10 Reasons Why Genotyping for Antiplatelet Therapy Is Not Needed

10. Compliance is key!
9. Metabolic pathways
8. Drug Interactions
7. Other Genes
6. Other Receptors
5. Clinical factors
4. Limited contribution
3. No RCT proof
2. Phenotype Rules!
1. Better drugs
Clopidogrel Pharmacogenomics: Will the FDA’s Black Box Change Practice?

Pro Argument – Clopidogrel-CYP2C19 Black Box Warning: The Elephant in the Room

Craig R. Lee, Pharm.D., Ph.D.
UNC Eshelman School of Pharmacy
UNC Institute for Pharmacogenomics & Individualized Therapy

ACCP Annual Meeting
Pittsburgh, PA
October 17, 2011
Personalized Medicine

Is this really a new concept?

**Definition**

- Integrating evidence generated at the population level (e.g., registries, RCT’s) into clinical decisions for individual patients.
  - Diagnostics, pharmacotherapy

**Can we integrate “omics” into what we already do?**

**The “Omics” Definition**

- Integrating “omics” technology into clinical decisions
  - Genomics, biomarkers (e.g., transcriptomics, proteomics, metabolomics)
Substantial Inter-Individual Variability in Clopidogrel’s Anti-Platelet Effect Exists

• “Residual” platelet activity (RPA) associated with higher risk of death, MI and stent thrombosis.
Clopidogrel Pharmacogenomics – PK/PD

Clopidogrel (pro-drug)

\[ CYP2C19^{*1} \] (wild-type)

Active metabolite

\[ CYP2C19^{*2} \]
- "Null" allele (no metabolic activity)
- Accounts for ~75-85% of CYP2C19 ‘poor metabolizers’ across populations
- Caucasian: 15% ; African-Am: 17% ; Asian: 30%
- \( CYP2C19^{*3} \) also has “null” function, but less common

Platelet Function
Clopidogrel Pharmacogenomics

Clopidogrel

CYP2C19*2

Active metabolite

Pharmacokinetic

(lower active metabolite exposure)

Platelet Function

Pharmacodynamic

(less inhibition of aggregation)
**CYP2C19 genotype predicts clinical outcome**

Validated in multiple populations (ACS, PCI)

<table>
<thead>
<tr>
<th>CV Death / MI / Stroke</th>
<th>Stent Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2C19 LOF Carrier vs. Wild-type</strong></td>
<td><strong>CYP2C19 LOF Carrier vs. Wild-type</strong></td>
</tr>
<tr>
<td><strong>TRITON-TIMI 38:</strong></td>
<td><strong>TRITON-TIMI 38:</strong></td>
</tr>
<tr>
<td>12.1% vs. 8.0%</td>
<td>2.6% vs. 0.8%</td>
</tr>
<tr>
<td>HR 1.53 (1.07-2.19)</td>
<td>HR 3.09 (1.19-8.00)</td>
</tr>
<tr>
<td><strong>Meta-analysis:</strong></td>
<td><strong>Meta-analysis:</strong></td>
</tr>
<tr>
<td>HR 1.57 (1.13-2.16), P=0.006</td>
<td>HR 2.81 (1.81-4.37), P&lt;0.001</td>
</tr>
</tbody>
</table>
FDA Labeling Changes
(June 2009)

• CYP2C19 variant alleles
  → impaired metabolism to active metabolite (PK)
  → less inhibition of platelet activation (PD)
  → higher risk of death / MI / stent thrombosis (outcome)

PRECAUTION

“... patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished anti-platelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function”
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 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)].
“Information regarding the predictive value of pharmacogenomic testing is very limited at this time”

“The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.”

“Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism (“poor metabolizers”) may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes.”

“If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered.”
Initiate antiplatelet therapy with standard dosing of clopidogrel if genotype unknown

**CYP2C19**

- **UM** (*1/*17, *17/*17)
  - Standard dosing of clopidogrel

- **EM** (*1/*1)
  - Standard dosing of clopidogrel

- **IM** (*1/*2)
  - Prasugrel or other alternative therapy

- **PM** (*2/*2)

Clopidogrel Pharmacogenomics

*What alternatives are available?*

- **Therapeutic switch**
  - Prasugrel (FDA approved July 2009) – ACS
  - Ticagrelor (FDA approved July 2011) – ACS
  - Ticlopidine (FDA approved 1991) – stroke, PCI

- **Increase clopidogrel dose**
  - 600-900 mg loading dose
  - 150 mg/day maintenance dose

- **Add an adjunctive therapy**
  - Cilostazol

- **Alter PCI strategy**
  - Use BMS instead of DES (lower stent thrombosis risk)
If a patient presented for PCI, and they were known to carry a \textit{CYP2C19*2} variant allele, what course of action would you take?