Pharmacogenomics and Warfarin Testing: The Case for Personalized Medicine

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Conflict of Interest Statement

I, Shiew-Mei Huang, PhD, declare no conflicts of interest or financial interests with any pharmaceutical manufacturers, medical device company, or in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Extrinsic

Drug–drug interactions

Intrinsic

Environment

Age
Race
Organ dysfunction
Disease
Pregnancy/lactation
Gender
Genetics
Others

Medical practice

Smoking/diet

Alcohol use

Regulatory

Others

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If evidence is available to support the safety and effectiveness of the drug only in *selected subgroups* of the larger population with a disease, the labeling should describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug.

*CFR 201.57*
### Comparative exposure and dose recommendation in subgroups with various patient factors

<table>
<thead>
<tr>
<th>Group</th>
<th>Ethnic factor</th>
<th>Fold change in exposure (AUC)</th>
<th>Initial dose (mg)</th>
<th>Daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>1-fold</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td>2</td>
<td>Hepatic impairment</td>
<td>1.1-fold (mild)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.2-fold (moderate)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td>3</td>
<td>Renal impairment</td>
<td>1-fold (mild)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-fold (moderate)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-fold (severe)</td>
<td>5</td>
<td>≤10</td>
</tr>
<tr>
<td>4</td>
<td>Race</td>
<td>2-fold (Asians)</td>
<td>5</td>
<td>5–20</td>
</tr>
<tr>
<td>5</td>
<td>Cyclosporine</td>
<td>7-fold</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Gemfibrozil</td>
<td>1.9-fold</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Lopinavir/ritonavir</td>
<td>5-fold</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from [http://www.accessdata.fda.gov/scripts/cder/drugsatfda.](http://www.accessdata.fda.gov/scripts/cder/drugsatfda.); **November 2007 labeling**

Recent Example
Dosage & Administration
Tetrabenazine

Dosing Recommendations above 50 mg per day Patients who appear to require doses greater than 50 mg per day should be genotyped for CYP2D6.

The dose of XENAZINE should be individualized.

Xenazine (Prestwick, tetrabenazine) labeling approved August 15, 2008
Post-marketing Labeling Changes
Public Debates

The Critical Path of Warfarin Dosing: Finding an Optimal Dosing Strategy Using Pharmacogenetics
LJ Lesko

Warfarin and Pharmacogenomic Testing: The Case for Restraint
DA Garcia


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Warfarin: Significant Problems for Humans!

- Ranks #1 in total mentions of deaths for drugs causing AEs from death certificates
- Ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding range from [0-2%] to [10-16%] (versus 0.1% for most drugs)
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 29% (% per year)

FOR IMMEDIATE RELEASE
August 16, 2007

FDA Approves Updated Warfarin (Coumadin) Prescribing Information

New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients
Finding Doses to Maintain Therapeutic Anticoagulation is Largely *Trial and Error*

**Dose Adjustments**
- No (5 mg) = 16%
- Yes (< 5 mg) = 51%
- Yes (> 5 mg) = 33%

*Reynolds KK et al. Personalized Medicine 2007*
Why Maintaining **Therapeutic INR Range** is Critical

INR Difficult to Maintain

INR (% patient-days)

<1.5  1.5-1.99  2-3  3.01-4  4.01-5  >5

INR

How can we control the variability in response?
Warfarin Pharmacokinetics (PK) & Pharmacodynamics (PD)

PK

Dose

Absorption

k_a

Tissue

PLASMAC

free

CL_2/V_1

CL_2/V_2

Elimination

PLASMAC

Response

VKORC1

Genotype

CYP2C9 Genotype

Age

Inducers, Inhibitors

INR

INR

Synthesis

k_{synth}

PCA

Degradation

k_{out}

PT


Predicting the Warfarin Stable Dose

Age, Gender, Drugs, BW, Race, Diet, Others

Genotypes (CYP2C9, VKORC1)

<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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Recent Development

Gage et al, *Clin Pharmacol Ther*, Epub Feb 27, 2008 (2C9+VKORC1)

Results of large prospective studies within the *International Warfarin Pharmacogenetics Consortium* are forthcoming

Prospective studies in different populations strongly suggest that pharmacogenetic-based dosing improves time to therapeutic INR and reduces ADRs

17-22% vs. 53-54%
clinical only vs. clinical + genetics
How do we dose patients with CYP2C9 and VKORC1 info?
Estimated therapeutic dose: 4.5 mg/day.

Today's prescribed dose: [ ] mg.

(Slide the Pointer to the dose you would like to prescribe today.)

Patient Code (e.g. BG or 007)*: [ ]

Email address to save patient under*: [ ]

When would you like an email to remind you to check the INR: In [ ] hours.

* All information entered into this site is kept confidential. Your e-mail address will not be shared, sold, or rented. It is required to save and to access this record.

Recommendations

We developed this initial dose algorithm from 1015 patients and prospectively validated in 292 additional patients starting warfarin where the R2 was 54% and the median absolute error was 1.0 mg/day ([Clin Pharmaco Ther] 2008).
Estimated dose of warfarin (mg/day) according to genotype for an “average” patient (65y.o., male, Caucasian, BSA 2.0, nonsmoker, no other drugs, Dx atrial fibrillation, target INR 2.5)

<table>
<thead>
<tr>
<th>VKORC1 genotype</th>
<th>CYP2C9 genotype</th>
<th>*1/*1</th>
<th>*1/*2</th>
<th>*1/*3</th>
<th>*2/*2</th>
<th>*2/*3</th>
<th>*3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td></td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3.5</td>
<td>3</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td>3</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

## Frequency of VKORC1

<table>
<thead>
<tr>
<th></th>
<th>1639 G&gt;A</th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caucasians</strong></td>
<td></td>
<td>19%</td>
<td>56%</td>
<td>25%</td>
</tr>
<tr>
<td>(N=297)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spanish</strong></td>
<td></td>
<td>32%</td>
<td>40%</td>
<td>28%</td>
</tr>
<tr>
<td>(N=105)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chinese</strong></td>
<td></td>
<td>80%</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>(N=104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>African</strong></td>
<td></td>
<td>0%</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Americans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=159)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asians may need a lower dose

Are tests readily available?
• There are four FDA approved tests (additional ones in review*) and numerous laboratory developed tests on the market
  [Approved: Nanosphere, Autogenomics, ParagonDx, Osmetech]

  ➔ Available tests providing results within 1 hour

• As the use increased, so would the availability of tests at POC

<*Personal communication- Steve Gutman; Courtney Harper; Lakshman Ramamurthy >
• Takes longer to reach therapeutic INR, stable dose
• Poor prediction of dose based on clinical data alone
• 70-75%* of patients not being treated in anticoagulation centers (daily INR not feasible, impractical & costly in private practice)
• 4,500-22,000 additional serious bleeding events annually

<Higashi JAMA, April 2002; Gage Clin Pharmacol Ther, September 2008; *estimate from Garcia- Anticoagulation Forum; McWilliams Pharmacogenomics, May 2008>
Minimize/Eliminate the uncertainties!!

How can it NOT help by incorporating additional information?
<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Drug products: generic (brand) names</th>
<th>Ethnicity information</th>
<th>Genetics information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiorenal</td>
<td>Isosorbide dinitrate–hydralazine (BiDil)</td>
<td>Indicated for self-identified blacks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin II antagonists and ACE inhibitors</td>
<td>Smaller effects in blacks&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Rosuvastatin (Crestor)</td>
<td>Lower dose for Asians</td>
<td>Dose adjustments for TPMT variants</td>
</tr>
<tr>
<td>Transplant</td>
<td>Azathioprine (Imuran)</td>
<td>Higher dose for blacks</td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>Trastuzumab (Herceptin)</td>
<td></td>
<td>Indicated for HER2 overexpression</td>
</tr>
<tr>
<td></td>
<td>Irinotecan (Camptosar)</td>
<td></td>
<td>Dose reduction for UGT1A1*28</td>
</tr>
<tr>
<td></td>
<td>6-Mercaptopurine (Purinethol)</td>
<td></td>
<td>Dose adjustments for TPMT variants</td>
</tr>
<tr>
<td></td>
<td>Erlotinib (Tarceva)</td>
<td></td>
<td>Different survival and tumor response in EGFR-positive and -negative patients reported</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Maraviroc (Selzentry)</td>
<td></td>
<td>Indicated for CCR5-positive patients</td>
</tr>
<tr>
<td></td>
<td>Oseltamivir (Tamiflu)</td>
<td>Neuropsychiatric events mostly reported in Japan</td>
<td>Boxed warning for HLA-B*5701 allele</td>
</tr>
<tr>
<td></td>
<td>Abacavir (Ziagen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Codeine</td>
<td></td>
<td>Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hematology</td>
<td>Warfarin (Coumadin)</td>
<td>Lower dose for Asians</td>
<td>Lower initial dose for CYP2C9- and VKORC1-sensitive variants</td>
</tr>
<tr>
<td>Psychopharmacological</td>
<td>Thioridazine (Mellaril)</td>
<td></td>
<td>Contraindication for CYP2D6 PM</td>
</tr>
<tr>
<td></td>
<td>Atomoxetine (Strattera)</td>
<td></td>
<td>Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM</td>
</tr>
<tr>
<td>Neuropharmacological</td>
<td>Carbamazepine (Tegretol)</td>
<td>Box warning for Asians with variant alleles of HLA-B*1502</td>
<td>Box warning for Asians with variant alleles of HLA-B*1502</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex. Data from [http://www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda).<sup>a</sup>A general statement in the candesartan (Atacand) labeling. <sup>b</sup>[http://www.fda.gov/cder/drug/infopage/codeine/default.htm](http://www.fda.gov/cder/drug/infopage/codeine/default.htm)
Additional Opportunities
According to SLCO1B1 rs4149056 Genotype

OATP1B1 & Myopathy (80 mg Simvastatin)

Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype

Cumulative No. and Percentages with Myopathy

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Population Frequency</th>
<th>Year 1 Attributable to genotype</th>
<th>Year 5 Attributable to genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>%</td>
<td>no.</td>
</tr>
<tr>
<td>TT</td>
<td>0.730</td>
<td>12</td>
<td>0.34</td>
</tr>
<tr>
<td>CT</td>
<td>0.249</td>
<td>17</td>
<td>1.38</td>
</tr>
<tr>
<td>CC</td>
<td>0.021</td>
<td>16</td>
<td>15.25</td>
</tr>
<tr>
<td>All genotypes</td>
<td>1.000</td>
<td>45</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Faster Metabolizers of nicotine benefit from bupropion

CYP2A6 genotype

\[\text{Patterson et al, Clin Pharmacol Ther. 84(3): 320-325, 2008}\]
CYP2C19 and Clopidogrel

Carriers: with at least one variant alleles, *2, 3, 4, 5, 8 (IM+PM);
*Outcome: a composite of death from cardiovascular causes, myocardial infarction, or stroke

PM: with two reduced function alleles
IM: one reduced function allele
EM: no variant alleles;
UM: one or two *17

Summary

• Variations in drug response may be attributed to various intrinsic and extrinsic factors

• It is important to assess safety, effectiveness and dose-exposure response in various subgroups during drug development and apply the results of exposure-response to better define optimum individual dosing regimens
Summary (2)

- FDA encourages early communications (e.g., FDA/industry early meetings, voluntary genomic submissions, guidances, best practices)

- As the pharmacogenetics/pharmacogenomics information becomes available; its association with the safe and effective use of drugs has been incorporated in the drug label
Summary (3)

- FDA has updated the warfarin label and approved/cleared genetic tests– some with rapid turnaround time

- More than a dozen publications showed value of genetic testing

- More tests being reimbursed by insurance
Summary (4)

- We have sufficient data to act and recommend genotyping at the initiation of warfarin.

- We should move from the present “trial & error” to more “educated prediction of individual dose”