Pharmacogenetic-Based Initial Dosing of Warfarin: Not Ready for Prime Time

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Availability of the human genome sequence offers the promise of personalized medicine through pharmacogenomics. Warfarin, a member of the coumarin family of oral anticoagulants used to prevent and treat thromboembolic disorders and one of the top 20 prescribed medications in the US, is an ideal drug for applying the principles of pharmacogenetics. Warfarin inhibits reduction of vitamin K epoxide by the vitamin K epoxide reductase complex, subunit 1 (VKORC1)2 enzyme, causing hypogammacarboxylation of vitamin K–dependent coagulation factors and an acquired coagulopathy. Warfarin therapy is monitored with the international normalized ratio (INR) derived from the prothrombin time. The INR therapeutic range is narrow, and the maintenance warfarin dose required to produce a therapeutic INR for an individual is both unpredictable and widely variable, leading to bleeding complications, especially during the initiation period when dose adjustments are made by trial and error (1).

During the past 12 years, discoveries regarding the molecular basis of warfarin pharmacokinetics and pharmacodynamics have been combined with clinical and demographic information from stably anticoagulated patients to generate many dosing algorithms. Up to 54% of the interpatient variation in therapeutic warfarin dose can be accounted for by the combination of patient age, body size, target INR, and use of amiodarone with the genotypes for 2 single-nucleotide polymorphisms (SNPs) in cytochrome 2C9 that reduce warfarin metabolism and 1 from a group of SNPs in the vitamin K epoxide reductase complex, subunit 1 (VKORC1)3 gene in high linkage disequilibrium and associated with increased sensitivity to warfarin (2).

Few pharmacogenetic algorithms have been validated, however, and all are less accurate when used to predict therapeutic warfarin doses in African Americans (3), most likely because of currently unknown genetic mechanisms that affect warfarin sensitivity. Ongoing molecular and translation research has identified additional genetic variants affecting warfarin dosing (4), but to date they are rare or have modest impact on therapeutic dose prediction.

In August 2007, the US Food and Drug Administration (FDA) added information to warfarin and Coumadin® package insert regarding lowering of therapeutic warfarin doses in cases involving the cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9) gene CYP2CP*2/*3 SNPs and the VKORC1 SNP, but the FDA did not recommend or require genotyping be performed before initiation of warfarin therapy. In response, to enable detection of warfarin pharmacogenetically relevant SNPs, the molecular diagnostic industry has developed reagents for real-time PCR instruments, fluorescent plate readers, and reagent-instrument platforms. To date, the FDA has licensed 5 tests, and others are currently under evaluation. In 2007, the College of American Pathologists added CYP2CP*2/*3 and VKORC1 SNPs to its pharmacogenetics proficiency testing panel. It would appear that there is considerable momentum from some stakeholders to adopt pharmacogenetic-based initial dosing of warfarin into routine clinical practice.

It would be reasonable to expect that more accurate, pharmacogenetic-based initial dosing of warfarin would reduce the risk of serious bleeding and thrombotic complications. A few retrospective cohort studies support an association between bleeding complications and CYP2C9 *2/*3 (5–7) but not VKORC1 SNPs associated with increased warfarin sensitivity (7). Only 3 small prospective randomized control trials have compared pharmacogenetic-based initiation of warfarin to empiric dosing (8–10) (Table 1), and the findings are not convincing. The studies used different algorithms and nomograms for genetic and control dosing arms, respectively, and measured different primary outcomes, including feasibility of rapid genotyping, time to first therapeutic INR, or percentage of out-of-range INRs. Only 1 trial identified a significant

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2 Nonstandard abbreviations: VKORC1, vitamin K epoxide by vitamin K epoxide reductase complex, subunit 1; INR, international normalized ratio; SNP: single nucleotide polymorphism; FDA, US Food and Drug Administration.
3 Human genes: VKORC1, vitamin K epoxide reductase complex, subunit 1; CYP2C9, cytochrome P450, family 2, subfamily C, polypeptide 9.
improvement in time within the therapeutic INR range (8) (Table 1). None was powered to detect a difference in serious bleeding complications.

Organizations representing clinical geneticists as well as cardiovascular physicians have recently provided position statements and recommendations regarding pharmacogenetic-based warfarin dosing. Based on a commissioned rapid ACCE (Analytical; clinical validity; clinical utility; and ethical, legal and social implications) review of this topic, a working group of the American College of Medical Genetics concluded that there is insufficient evidence to recommend for or against routine CYP2C9 and VKORC1 genotyping (11). The American College of Chest Physicians Antithrombotic and Thrombolytic Therapy Guideline, eighth edition, concluded there was insufficient evidence to support pharmacogenetic-based determination of initial dosing of warfarin (12). The Center for Medicare and Medicaid Services sought public input about pharmacogenetic testing by adding the issue to its 2008 national coverage determination dialog topics, using warfarin pharmacogenetics as an example of a potential application lacking high-quality evidence from clinical trials about its clinical utility.

Consistent calls for additional trials to evaluate the clinical utility of pharmacogenetic-based warfarin dosing are being addressed by the National Heart Lung and Blood Institute’s funding of a prospective, multicenter randomized controlled study. The COAG (Clarification of Optimal Anticoagulation through Genetics) trial, scheduled to begin in early 2009, will randomize patients beginning warfarin therapy to initial dosing determined with algorithms including genotype and clinical data or clinical data only. Patients and physicians will be blinded to which algorithm is being employed, and dose adjustments based on subsequent INR results will be protocol driven. The goal of the COAG trial is to assess the incremental effects of using genetic information on anticoagulation control. The decision to use a laboratory outcome as the primary endpoint in the COAG trial is based on evidence that improved therapeutic INR control is associated with reduced bleeding and thrombotic complications and medically related costs (13). Although this study is not powered to detect differences in bleeding and thrombotic complications between the 2 initial dosing algorithms, these adverse events will be assessed and reported. Other investigators are planning to conduct

### Table 1. Randomized control trials of pharmacogenetic-based initial warfarin dosing: impact on time within therapeutic INR range.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Patients</th>
<th>White, %</th>
<th>Genotyped SNPs</th>
<th>Initial warfarin dosing</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillman (10)</td>
<td>38</td>
<td>100</td>
<td>CYP2C9*2/*3</td>
<td>d.1: PGx algorithm</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>d.:=2: INR-based nomogram</td>
<td></td>
</tr>
<tr>
<td>Caraco (8)</td>
<td>191</td>
<td>100</td>
<td>CYP2C9*2/*3</td>
<td>d.1: *1/*1: 1.25 × control arm dose</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Variants dosed at a percentage of *1/*1 dose</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*1/*2: 80%</td>
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<td></td>
<td>*1/*3: 60%</td>
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<td></td>
<td></td>
<td></td>
<td>*2/*2: 50%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>*2/*3: 40%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*3/*3: 15%</td>
<td></td>
</tr>
<tr>
<td>Anderson (9)</td>
<td>206</td>
<td>94</td>
<td>CYP2C9*2/*3</td>
<td>d.1-2: 2 × PGx algorithm</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VKORC1 1173c</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>d.3-4: PGx algorithm</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>d.:=5: INR-based nomogram</td>
<td></td>
</tr>
</tbody>
</table>

* d. day; PGx, pharmacogenetic-based.
* P < 0.001.
* In high linkage disequilibrium with VKORC1 promoter SNP at position –1639.
similar prospective studies in the US and abroad, and it is likely that pooling of results in the future will enable an accurate assessment of the impact of pharmacogenetic-based initial dosing of warfarin on serious bleeding and thrombotic events.

Given that the clinical efficacy of pharmacogenetic-based dosing of warfarin lacks compelling evidence based on well designed and adequately powered prospective trials, it would be a leap of faith to assume that pharmacogenetic-based dosing would be more effective, i.e., safer, than empiric, clinically based initial dosing of warfarin as currently practiced, or to estimate the cost vs benefit of routine genotyping when starting a patient on warfarin. It will likely be several years until enough information is available to arrive at a consensus. Until then, however, to prematurely encourage or require pharmacogenetic testing of CYP2C9 and VKORC1 alleles by either regulatory or reimbursement entities could tarnish the future of evidenced-based personalized genomic medicine by preventing recruitment for important studies such as the COAG trial.

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References