PERSPECTIVES

POINT/COUNTERPOINT

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

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"Great truths may be very near, and yet not be discerned."
—Sir James Paget, surgeon and pathologist, 1879

In 2004 and 2005, side effects from just three drugs were responsible for a full third of all U.S. emergency room visits by senior citizens who had adverse reactions to medications. Warfarin was one of these drugs, accounting for 58,000 emergency room visits a year in those 65 and older.[1] The Adverse Event Reporting System of the US Food and Drug Administration (FDA) provides evidence that warfarin is among the top 10 drugs with the greatest number of serious adverse events. Literature reports of major bleeding frequencies for warfarin vary from as low as 0% to as high as 16% (refs. 2, 3). On the basis of these data, the FDA added a new black-box warning to the warfarin label in 2006.

A scientific and clinically rational approach to optimal dosing of warfarin

Optimal dosing of warfarin during the induction phase is a multidimensional challenge. A common dosing strategy is to prescribe 5 mg of warfarin per day and adjust the dose based on international normalized ratio (INR) values. This is an inefficient process because there are significant interpatient differences in the pharmacokinetics and pharmacodynamics of warfarin that influence INR response. These differences cannot be predicted by clinical factors alone. As a result, patients experience delays in achieving stable maintenance doses and therapeutic INR values.

Numerous clinical studies have found that genetic differences between patients are important determinants of optimal dosing. Common single-nucleotide polymorphisms in the cytochrome P450 2C9 (*CYP2C9*) gene influence the pharmacokinetics of warfarin, and single-nucleotide polymorphisms in the vitamin K epoxide reductase gene (*VKORC1*) influence the pharmacodynamics of warfarin. These genetic factors alone account for 30–35% of the variability in warfarin dosing, whereas clinical factors explain only 17–21% of the variability.[4] Dosing algorithms that combine genetic and clinical factors can predict up to 55% of the variability in stable maintenance doses even without INR values. By adding INR values after three warfarin doses, up to 79% of the variability can be explained using a combined genetic and clinical dosing algorithm.[5] One such algorithm is available at http://www.warfarindosing.org.

Why should pharmacogenetic-guided dosing improve the efficiency and safety of warfarin anticoagulation?

Two of the most important determinants of the effectiveness and safety of warfarin are (i) time in the therapeutic INR range (TTR) and (ii) the intensity of anticoagulation (INR >3–4).[6] Fluctuations above or below the therapeutic range are most probable during the induction phase of warfarin dosing, which is associated with a greater risk of bleeding events.[7,8]

Genetic risk factors play an important role during the induction phase. Limdi *et al.* reported that the risk of hemorrhagic complications was 5.3-fold higher before stabilization of warfarin therapy and 2.2-fold higher after stabilization in individuals who were carriers of the variant *CYP2C9* genotype.[9] Schwarz *et al.* reported that a majority of bleeding events due to warfarin occurred within the first 28 days. Among these patients, 75% (9/12) had at least one variant *VKORC1* gene and 50% had at least one variant of the *CYP2C9* gene.[10]

By taking individual genetic factors into account along with clinical factors, the dosing of warfarin during the induction phase can be made significantly better than, for example, an empirical dose of 5 mg.

Caraco *et al.*[11] compared *CYP2C9* genotype-guided dosing (study group) to non–genotype-guided dosing (control group) and showed the following benefits of genotyping for patients and health-care providers:

1. Reduction of the time to stable anticoagulation from 32 days to 14 days
2. Improvement of the TTR from 63.4% to 80.4%

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3. Reduction of minor bleeding episodes from 12.5% to 3.2%
4. Reduction of the time above INR >3 from 6.58 days to 1.77 days
5. Reduction of the number of INR measurements from 10.7 to 4.9

Furthermore, none of the 35 carriers of a variant *CYP2C9* allele in the study group had an INR >4, whereas 5 of 44 carriers in the control group had an INR >4.

The Schwarz study had two primary study outcomes: the time to first INR >4 and the time above the INR therapeutic range.[10] The results of this study showed that:

1. The time to first INR >4 occurred significantly earlier (17 days vs. 23 days) in patients who had the A/A haplotype of *VKORC1* (homozygous, "high sensitivity") when compared with the non-A/non-A haplotype (homozygous, "low sensitivity"). The adjusted hazard ratio for the A/A haplotype for time to first INR >4 was 2.52.
2. Patients who had the A/A *VKORC1* haplotypes spent twice as much time (18% vs. 9%; $P < 0.05$) above the therapeutic INR range as those with the non-A/non-A haplotype.
3. Patients with at-risk *CYP2C9* genotypes (*2/*2, *3/*3 and *2/*3) experienced shorter times to the first INR >4 (18 days vs. 22 days). The adjusted hazard ratio for these patients was 2.67.

Anderson *et al.*[12] conducted a clinical study to validate a warfarin dosing algorithm by comparing pharmacogenetics-guided dosing using knowledge of *CYP2C9* and *VKORC1* genetics (PG-guided) with usual clinical care dosing without genetic testing. This trial is often misrepresented as a "negative study" because the primary end point—a reduction in the percentage of INR measurements falling outside of the therapeutic range in the *total population*—did not differ statistically between the two arms (30.7% vs. 33.1%). The authors attributed this result to the in-hospital initiation of warfarin therapy with aggressive management by an experienced and dedicated anticoagulation service. However, the study provided the following results supporting the use of genetic testing:

1. The patients who stand to benefit the most from PG-guided dosing represent 60% of the total population who are potentially at risk for over- and under-anticoagulation.
2. Patients with no gene variants needed more than 5 mg/day; patients with multiple gene variants needed at least 25% less than 5 mg/day.
3. The average stable maintenance dose in patient subgroups was defined by their number of variant alleles. The relationship between dose and number of alleles was linear between zero and four variants, with doses ranging from 45 mg/week (patients with zero variants) down to 8 mg/week (patients with four variants).
4. The PG-guided arm identified initial induction doses that were significantly more predictive of the stable maintenance doses based on per-patient average deviation between the two; for example, for wild-type allelic patients the change in dose for the PG-guided arm was 9.1 mg/week vs. 16.1 mg/week for the standard arm without PG.
5. Patients in the PG-guided arm required fewer and smaller dose adjustments and fewer INR measurements than those in the usual clinical care arm (7.2 vs. 8.1) when followed for up to 3 months.

The number of dosing adjustments during the induction phase may potentially be an important risk factor that requires further investigation. Preliminary results from the Medco-Mayo study have shown that 73% of the first 112 patients studied required dosing adjustments after starting warfarin; 22% of patients starting warfarin with one or no dosing adjustments and followed for 6 months were hospitalized because of a clot or a bleeding episode. Patients who required two or more dosing adjustments had a 30% hospitalization rate.[13]

Numerous studies, including those mentioned above and a meta-analysis of nine other studies, have provided considerable evidence that gene variants in both *CYP2C9* and *VKORC1* significantly influence the quality and efficiency of anticoagulation and that prospective measurement of genotype would have the greatest potential impact during the induction phase of warfarin therapy.[14,15] These studies have been reported across various racial or ethnic groups and from different continents. Thus far no studies have shown PG-guided dosing to be *inferior* to clinical care without PG.

Even though PG-guided initial doses seem to be closer to stable maintenance doses, it should be emphasized that they do not predict 100% of warfarin dose requirements. Therefore, an *adaptive* dosing strategy using INR values is still required to fine-tune the induction doses and efficiently achieve maximal TTR.

Cost-effectiveness of warfarin gene tests

Genetic testing for warfarin need be done only once and ideally in patients first starting warfarin. The cost of testing for both genes varies but is approximately $250 per gene, not unlike the cost of other specialty laboratory tests. Because rapid performance of *CYP2C9* and *VKORC1* assays (1- to 24-hour) is technically feasible, individualization of warfarin starting doses can be done in real time without significant inconvenience to either patient or health-care provider.

A recent attempt has been made to estimate the health-care savings from individualizing warfarin therapy using genetic testing.[16,17] The assumptions for this study were based primarily on serious or life-threatening bleeding events (defined as requiring treatment or medical evaluation) identified by Higashi *et al.*, who reported a bleeding rate of 28% in patients with *CYP2C9* gene variants vs. 13% in patients without *CYP2C9* gene variants.[18] The projected per-patient savings was $900. The authors conducted a sensitivity analysis using Monte Carlo simulations to show the range of net health-care savings between best-case and worst-case scenarios. There has been some controversy over the assumptions inherent in the cost-saving model, so more work must be done to obtain greater precision in estimating the cost-effectiveness. In future studies, it will be important to capture the potential savings from a reduction in the number of dosing

adjustments and a decrease in the number of INR measurements. These could translate into lower health-care costs meaningful to physicians and patients and related to the costs of INR testing, laboratory personnel time, providers' care time, and patients' time and inconvenience.

In summary, warfarin is widely used around the world, and its adverse effects represent a major risk to public health. All of us in health care want to do the best for our patients. Quality improvements in any area of clinical care are rarely simple, and adding PG testing is no exception.[19] Additional clinical trials of warfarin will and should be performed, to learn incrementally more about additional genetic and clinical factors important to (i) determining dose–response and/or clinical outcomes, especially in African-American, Asian, and Hispanic patients; (ii) defining a more precise approach to optimal initial dosing, and (iii) determining the cost-effectiveness and incremental improvement in quality of care rendered by *CYP2C9* and *VKORC1* testing.

The question about warfarin pharmacogenetics before us now is not "is it ready for prime time?" The more important question is, while more and more studies are being planned and/or conducted, should we accept and use our current knowledge about genetic factors to improve the quality of warfarin initial dosing and anticoagulation in our patients. The benefits and risks of pharmacogenetics, in my view, favor pharmacogenetics.

"Le mieux est l'ennemi du bien." (The perfect is the enemy of the good.)
—François-Marie Arouet (Voltaire), writer and philosopher, 1764

CONFLICT OF INTEREST
The author declared no conflict of interest.

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Warfarin and Pharmacogenomic Testing: The Case for Restraint

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Less than 5 years ago, the Human Genome Project culminated in the complete sequencing of the human genetic code. This impressive and labor-intensive accomplishment has left all of us in the medical profession with many hopes. However, although the possibility that we might use genetic testing to reduce the bleeding hazard associated with warfarin therapy is very exciting, the available evidence does not support the adoption of such testing in routine clinical practice.

There is widespread agreement that patients with certain variations in the genes encoding the CYP2C9 and VKORC1 enzymes require lower maintenance doses of warfarin. The evidence supporting this association is abundant and has been reviewed elsewhere.[1] However, despite the excitement that has been generated by years of elegant scien-

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