Warfarin Initiation and the Potential Role of Genomic-Guided Dosing

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Substantial inter-patient variability exists in the anti-thrombotic response to warfarin. This statement, an observation well known among clinicians and investigators, is a reflection of the wide range of warfarin maintenance doses observed across the population, often ranging anywhere from 1 mg/day to 20 mg/day. Consequently, warfarin therapy requires intensive monitoring via the International Normalized Ratio (INR) to guide its dosing, to maintain a therapeutic level of anti-thrombosis and to minimize the risk of bleeding.¹

Most would agree that once anti-thrombotic stability is attained and a maintenance dose is identified, clinicians are effectively able to maintain a therapeutic INR and minimize adverse bleeding. However, the initiation phase of warfarin therapy, the time when a patient's chronic maintenance dose requirement is unknown, remains the critical dosing period with the greatest degree of uncertainty and risk for adverse events. Over the years, clinicians have utilized demographic and clinical information such as age, concomitant medication use and dietary vitamin K intake, as well as various dosing nomograms to help predict an individual patient's warfarin dose requirement and to quickly attain a therapeutic INR.¹ Unfortunately, substantial inter-patient variability in warfarin sensitivity, in addition to its narrow therapeutic window, often lead to extended periods of sub- or supra-therapeutic dosing which are associated with increased risk of thrombotic or bleeding events, respectively. Identification of other factors that account for this variability in response, particularly during the initiation of therapy, could significantly shorten the dose titration period and ultimately reduce the risk of adverse events.

Clinical and molecular investigations have demonstrated that variability in both warfarin pharmacokinetics and pharmacodynamics contributes significantly to the observed variability in dose requirement. Warfarin inhibits vitamin K-dependent clotting factor synthesis via inhibition of vitamin K epoxide reductase complex 1 (*VKORC1*) and is primarily eliminated via cytochrome P450 2C9 (CYP2C9)-mediated metabolism. Alteration of these pharmacokinetic and/or pharmacodynamic pathways via a drug-drug interaction can significantly influence a patient's dose requirement.

Keywords:

Warfarin,
Anticoagulation,
Pharmacogenetics,
Pharmacokinetics,
CYP2C9,
Adverse events,
Multivariate dosing models,
Prothrombin time

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More recently, various retrospective studies have demonstrated that certain genetic polymorphisms in *CYP2C9* and *VKORC1* also significantly influence warfarin dose requirement. Higashi and colleagues² demonstrated that patients carrying a variant *CYP2C9**2 or *3 allele had significantly lower warfarin maintenance dose requirements compared to *CYP2C9**1/*1 (wild type) individuals and were at higher risk of a supratherapeutic INR, required a longer period of time to achieve stable dosing and were significantly more likely to experience a bleeding event during the initiation of therapy. Rieder and colleagues³ subsequently demonstrated that genetic variation in *VKORC1* also significantly influenced warfarin maintenance dose requirements accounting for a greater proportion of the variability in dose than *CYP2C9* genotype. Collectively, the results of these and other investigations suggest that *CYP2C9* and *VKORC1* genomic information, in addition to established factors such as age and concomitant medications, may be clinically useful during the initiation of warfarin therapy when the maintenance dose requirement is unknown and patients are at the greatest risk for adverse bleeding events. However, the clinical utility of a genomic-guided dosing strategy remains to be evaluated in large, prospective clinical trials.

Prior to completion of such prospective studies, we first need to: (1) determine the feasibility of obtaining and incorporating genomic information into warfarin dosing nomograms during the initiation of therapy, and (2) better understand the relative contribution of genomic and non-genomic factors to the warfarin dose-response relationship during this initiation period. Studies by Hillman, Wilke and colleagues (Hillman et al.⁴ and Wilke et al.⁵) published in *Clinical Medicine & Research* have provided important insight into these critical questions.

First, Hillman and colleagues⁴ demonstrated that prospective implementation of a genomic-guided dosing nomogram in patients being initiated on warfarin therapy is feasible, such that both patients and physicians are willing to participate and that the incorporation of genomic information into an individualized dosing strategy can occur in a timely and efficient manner (the average turnaround time from blood collection to genotype determination and dose calculation was approximately 4 hours). Although this single-center pilot study was underpowered to evaluate clinical outcomes such as bleeding events, the findings do suggest that genomic-guided dosing may be superior to standard approaches at predicting a patient's maintenance dose requirement, particularly in individuals with a variant *CYP2C9* allele.

Second, using a novel mathematical modeling approach, Wilke and colleagues⁵ extensively characterized the influence of various genomic and non-genomic factors on the warfarin dose-INR response relationship during the initial 30 days of therapy. This approach provided important insight into the relative contribution of individual patient factors such as dose, age, comorbidities, concomitant medication use and *CYP2C9* genotype on the rate of anticoagulation in a real-world patient

population, reinforcing the importance of factors such as age and concomitant medication use on warfarin sensitivity. Moreover, their extensive modeling of this mathematical relationship will undoubtedly improve the accuracy and generalizability of future multivariate dosing nomograms similar to the one utilized in their feasibility study.⁴ Importantly, future studies will be necessary to evaluate the influence of genetic variation in *VKORC1* on this dose-response relationship during the initiation phase of therapy.

The ultimate goals of pharmacogenomics is to account for and to minimize inter-individual variability in drug response, to maximize beneficial and minimize adverse drug effects and, ultimately, to improve clinical outcomes. In time, the aforementioned statement of clinical observation may be revised to: *The routine implementation of genomic and clinical data into individualized dosing strategies has accounted for a substantial proportion of inter-patient variability in warfarin sensitivity and has improved outcomes.* Although the need remains for additional prospective studies in larger populations that will evaluate the influence of such genomic-guided dosing strategies on the risk of clinical outcomes, such as bleeding events, the investigations by Hillman, Wilke and colleagues^{4,5} have taken a critical next step towards potential implementation of such strategies into clinical practice.

References

1. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):204S-233S.
2. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE. Association between *CYP2C9* genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA* 2002;287:1690-1698.
3. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, Blough DK, Thummel KE, Veenstra DL, Rettie AE. Effect of *VKORC1* haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005;352:2285-2293.
4. Hillman MA, Wilke RA, Yale SH, Vidaillet HJ, Caldwell MD, Glurich I, Berg RL, Schmelzer J, Burmester JK. A prospective, randomized pilot trial of model-based warfarin dose initiation using *CYP2C9* genotype and clinical data. *Clin Med Res* 2005;3:137-145.
5. Wilke RA, Berg RL, Vidaillet HJ, Caldwell MD, Burmester JK, Hillman MA. Impact of age, *CYP2C9* genotype, and concomitant medication on the rate of rise for prothrombin time during the first 30 days of warfarin therapy. *Clin Med Res* 2005;3:207-213.

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