European Journal of Pharmaceutical Sciences xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Review

Genotype-guided dosing of warfarin through modeling and simulation

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ARTICLE INFO

Keywords:
Warfarin
Pharmacogenetics
Pharmacometrics
Dosing nomogram
Precision medicine

ABSTRACT

Current genotype-guided algorithms for warfarin dosing fail to deliver optimal performance in two aspects: 1) these algorithms are not able to achieve the same level of benefits in non-white populations, since they were developed based on multivariate regression analysis with mostly European/White data and did not include genetic variants found frequently in non-white populations; 2) these algorithms do not account for the dynamic dose/response relationship and were limited in their usefulness to guide dosing during the initiation phase, as the possession of variant *VKORC1* and/or *CYP2C9* polymorphisms has been associated with a more rapid attainment of target international normalized ratio (INR) and higher risk of over-anticoagulation even in genotype-guided patients. To address these shortcomings, we report on the novel use of a previously published kinetic/pharmacodynamic (K/PD) model to develop a warfarin dosing nomogram to be used across genotypes and ethnicities. Our approach leverages data from both ethnically diverse and European patients, while accounting for the differential dose/response behaviors due to *VKORC1* and *CYP2C9* genotypes. According to simulations, the utilization of our dosing nomogram could enable effective attainment of therapeutic INR within one week in both ethnically diverse and European populations, while maintaining uniform INR response profiles across genotypes. Furthermore, in silico clinical trial simulations using the K/PD model could be a feasible approach to help to further refine our dosing nomogram to be more applicable in the clinical setting and explore possible outcomes even before prospective clinical trials are initiated.

1. Overview

This manuscript is part of an honorary issue for Professor Meindert Danhof. Professor Danhof has been a visionary and thought leader in the field of quantitative clinical pharmacology for over three decades and has developed many innovative pharmacokinetic-pharmacodynamic (PK-PD) concepts that are now routinely employed for rational drug discovery and development. The mechanistic nature of these concepts differs from conventional PK-PD approaches in that they contain specific expressions to characterize, in a strictly quantitative manner, processes along the causal pathway between drug administration and effect (Fig. 1) (Danhof et al., 2007). This includes target site distribution, target binding and activation, pharmacodynamic interactions, transduction, and homeostatic feedback mechanisms. Particularly the incorporation of concepts from receptor theory and dynamical systems analysis has yielded models with much improved properties for extrapolation and prediction. They also constitute the theoretical basis for a novel biomarker classification system that distinguishes between seven different groups of biomarkers: type 0, genotype/phenotype determining drug response; type 1, concentration of drug or drug metabolite; type 2, molecular target occupancy; type 3, molecular target activation; type 4, physiological measures; type 5, pathophysiological measures and type 6, clinical rating scales (Danhof et al., 2005). In combination, these biomarkers provide comprehensive information on the dynamic interaction between the drug, the biological system, and the disease.

Following a brief introduction, we will use the concepts outlined by Danhof et al. to review and evaluate current dosing approaches for warfarin. Although warfarin has been one of the most widely prescribed anticoagulants world-wide for many decades, optimal dosing is challenging due to its narrow therapeutic window and large between-subject variability in response to warfarin treatment, which results in either

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http://dx.doi.org/10.1016/j.ejps.2017.05.017
Received 8 May 2017; Accepted 10 May 2017

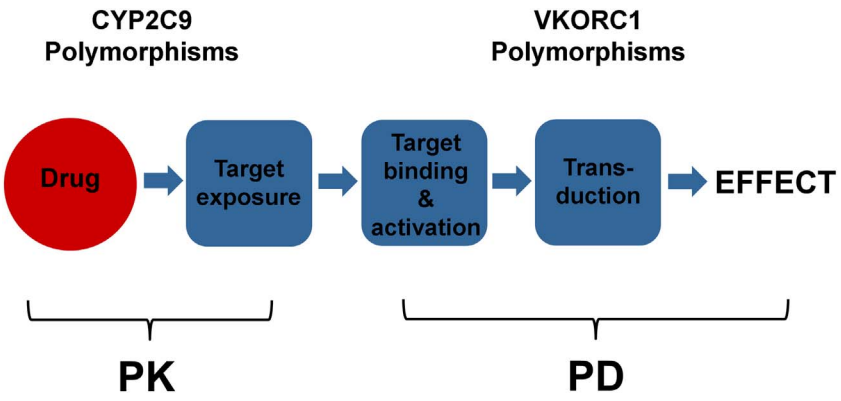

Fig. 1. Conceptual causal pathway of warfarin dose/response relationship.

insufficient anticoagulation or increased bleeding risk.

2. From rat poison to popular anticoagulant

While initially being introduced as a rodenticide in 1948, warfarin was later developed as an anticoagulant following an incident where a US soldier who attempted suicide by taking an overdose of the "rat poison" was successfully rescued by vitamin K treatment (Link, 1959; Wardrop and Keeling, 2008). Nowadays, warfarin is one of the most widely prescribed drugs and accounts for approximately 35 million prescriptions annually (Barnes et al., 2015; Desai et al., 2014; Kirley et al., 2012). However, as warfarin is a narrow therapeutic index drug, inappropriate dosing of warfarin can greatly increase the risk of thromboembolism, bleeding, hospitalization, and even death, especially during the initial months of therapy (Connolly et al., 2008; Hylek et al., 2007; Veeger et al., 2005; White et al., 2007; Wittkowsky and Devine, 2004). Although there have been newer alternative anticoagulants approved in recent years, these agents actually have similar if not higher bleeding risk to that of warfarin, while there are no FDA-approved reversal agents for most of these drugs (Kanagasabapathy et al., 2011). Furthermore, the high cost and copays of these newer anticoagulants presents barriers for their widespread use in certain socioeconomic populations, such as low-income patients and patients without private insurance (Desai et al., 2014; Kirley et al., 2012; Steinberg et al., 2013). Thus, warfarin continues to be the mainstay of oral anticoagulation at least for a large percentage of the patient population in the foreseeable future.

Given as a racemic mixture, warfarin is completely absorbed in the body and attains its C_{max} within 4 h post-dose after oral administration (Johansson et al., 2005; Walker et al., 2009). The anticoagulant effect of warfarin is exerted through the inhibition of vitamin K epoxide reductase, sub unit C1 (*VKORC1*). It effectively interferes with the

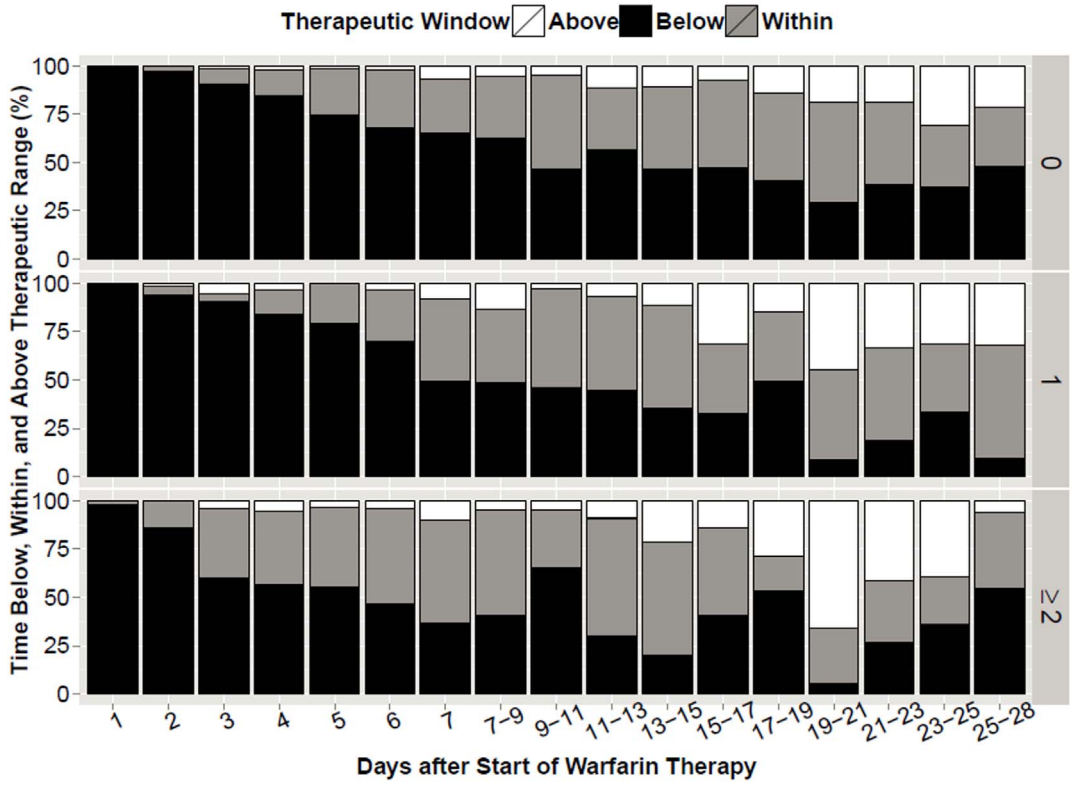

Fig. 2. Percent time in INR range (as calculated by Rosendaal method (Rosendaal et al., 1993)) that is *i)* below 2 (black) *ii)* within 2 to 3 (gray) and *iii)* above 3 (white) for patients with 0, 1, and ≥ 2 variant *VKORC1* (i.e. -1639G > A) and/or *CYP2C9* (i.e. **2, *3, *5, *6, *11, *14*) alleles (Reproduced with permission from CPT (Arwood et al., 2016)). Note: patients with *VKORC1* (i.e. -1639 > A) polymorphisms are pharmacodynamically more sensitive and thus have lower dose requirements, while patients with *CYP2C9* polymorphisms (i.e. **2, *3, *5, *6, *11, *14*) have reduced clearance of S-warfarin and require lower doses as well.

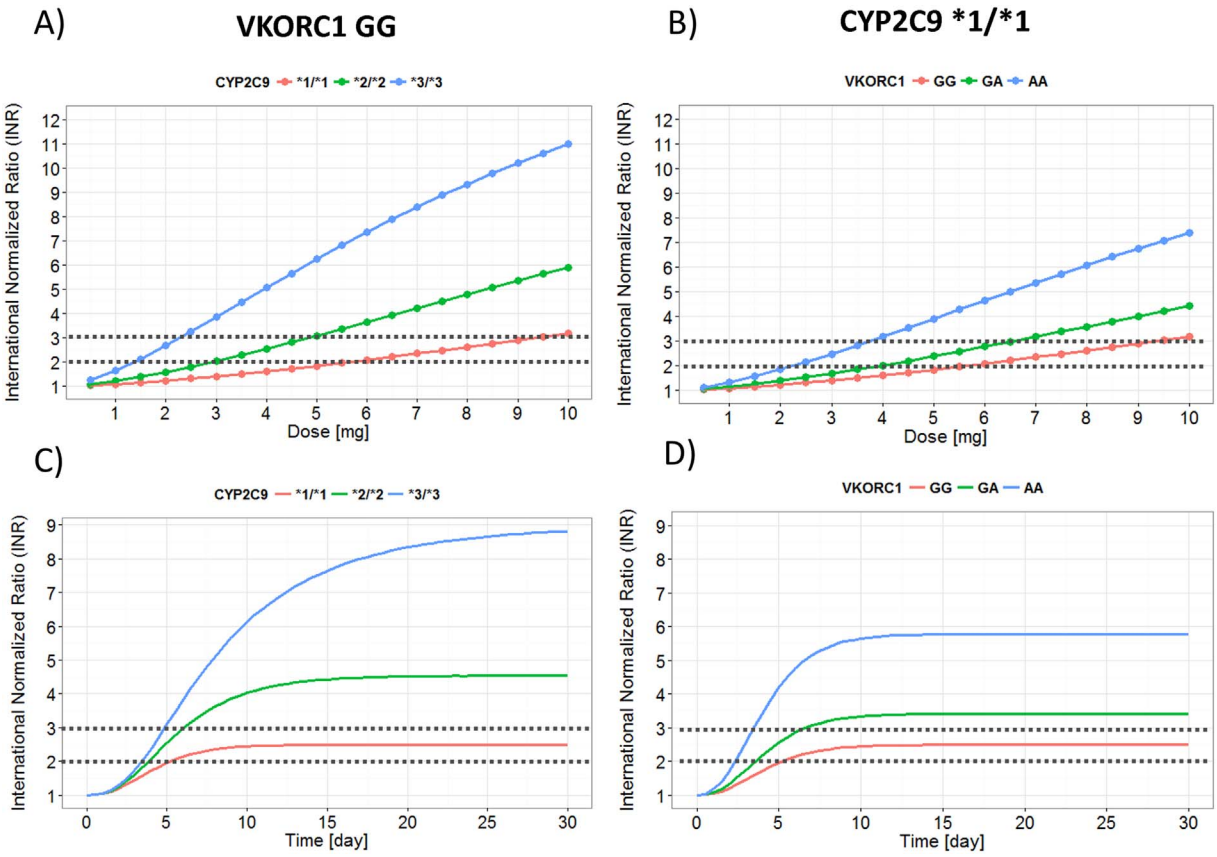

Fig. 3. Genotype differences in warfarin dose/response as illustrated by simulations performed using K/PD model by Hamberg et al. (Hamberg et al., 2010): A) simulated steady-state INR in typical *VKORC1* GG patients with different *CYP2C9* genotypes (**1/*1, *2/*2,* and **3/*3*) receiving varying daily doses (0.5 to 10 mg); B) simulated steady-state INR in typical *CYP2C9 *1/*1* patients with different *VKORC1* genotypes (GG, GA, and AA) receiving varying daily doses (0.5 to 10 mg); C) simulated INR curves over time in typical *VKORC1* GG patients with different *CYP2C9* genotypes (**1/*1, *2/*2,* and **3/*3*) receiving fixed doses of 7.6 mg q.d. (for achieving a steady-state INR of 2.5 in a typical *CYP2C9 *1/*1* and *VKORC1* GG patient); D) simulated INR curves over time in typical *CYP2C9 *1/*1* patients with different *VKORC1* genotypes (GG, GA, and AA) receiving fixed doses of 7.6 mg q.d. Note: dashed lines indicate therapeutic window of INR 2–3.

recycling of oxidized vitamin K to its reduced form, which is required for the activation of coagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C, S, and Z (Bell and Caldwell, 1973; Hamberg et al., 2007; Hirsh et al., 2001). Given that warfarin inhibits the production of coagulation factors and that factor II has a half-life of about 60 h, the full anticoagulant effects of warfarin are delayed until factor II reaches pharmacodynamic (PD) steady state (Wright et al., 2011). It is reported that S-warfarin is 3–5 times more potent than its stereoisomer for inhibiting *VKORC1* and is primarily cleared by the polymorphic enzyme *CYP2C9* (Aithal et al., 1999; Fasco and Principe, 1982; Scordo et al., 2002). Therefore, polymorphisms in *VKORC1* and *CYP2C9* are important factors that affect the PK and PD of warfarin. Consequently, both genotypes have to be considered in conjunction with other non-genetic factors, such as age, body surface area (BSA), concomitant medications, and smoking status, in order to optimally dose warfarin.

3. Warfarin dosing then and now

Traditionally, warfarin is started with a fixed dose of 5 mg/day with adjustments based on international normalized ratio (INR) response. Typical clinical practice for a patient starting warfarin therapy requires frequent monitoring of INR until the therapeutic range (2 to 3) is reached and maintained for at least 2 consecutive days (Kuruvilla and Gurk-Turner, 2001; Wigle et al., 2013). Significant strides in research have been made over the past decade, and there are examples of genotype-guided dosing entering into clinical practice that utilizes the available knowledge on the impact of genetic polymorphisms in *CYP2C9* and *VKORC1* on warfarin PK and PD, respectively, for optimal warfarin dosing (Nutescu et al., 2013; Van Driest et al., 2014). The Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines in 2011, which strongly recommend the use of genotype tailored dosing for patients when genotype information is available with the use of pharmacogenetic-guided dosing algorithms such as those by the International Warfarin Pharmacogenetics Consortium (IWPC) or Gage et al. (warfarindosing.org) (Gage et al., 2008; Johnson et al., 2011; Klein et al., 2009). These algorithms were derived from multivariate regression analyses and correlate therapeutic warfarin doses with clinical (age, body surface area, concomitant medications, smoking status, etc.) and genetic factors (*VKORC1* -1639G > A and *CYP2C9* polymorphisms). Compared to a fixed dose approach, their use was associated with better control INR in an European study (EU-PACT), and prior studies suggest they lead to a significant reduction in the risk for serious bleeding or thromboembolism in this population (Anderson et al., 2012; Epstein et al., 2010; Pirmohamed et al., 2013). On the other hand, results from the COAG (Clarification of Optimal Anticoagulation through Genetics) trial, which compared warfarin dosing with a pharmacogenetics versus clinical dosing algorithm in a more diverse population (27% African Americans and 6% Hispanics), showed no difference between dosing strategies in the population overall and worse anticoagulation control with genotype-guided dosing in African Americans (Kimmel et al., 2013). One explanation for the results in African Americans is that the pharmacogenetics dosing algorithm did not contain many genotypes important for this population, and recent evidence suggests that failure to account for these genotypes leads to significant over-dosing in African Americans

Table 1
A) Pharmacogenetics-based loading dose grid[†] according to *VKORC1* and *CYP2C9* genotypes to be used for days 1 and 2; B) Pharmacogenetics-based dose grid[†] in maintenance dose calculation to be used starting on day 3; C) Dose-adjustment nomogram during warfarin initiation. All doses are determined by assuming a normal INR value of 1 prior to initiation. [Δ] Based on the relative difference in clearances (Liu et al., 2012), reduction in dosing by 30% is recommended for *CYP2C9* *1/*8 or *8/*8 (found in African Americans), as compared to *1/*1. [†]Rounded to the nearest 0.25 mg. (Reproduced with permission from CPT (Arwood et al., 2016)).

A)

		CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*1/*8 or *8/*8 [Δ]	*2/*2	*2/*3	*3/*3
GG	9	9	9	6.25	6.5	6.5	6.5
GA	9	6.5	6.5	6.25	5	5	5
AA	3	3	3	2	3	3	3

B)

Maintenance dose (mg) = "Pharmacogenetics-based dose grid" – 0.01 × age

GG	8	6	5.5	5.5	3.75	2.75	2.5
GA	6.25	4.75	4.0	4.25	2.75	2.5	2.0
AA	3	2.5	2.5	2	2.25	1.75	1.5

C)

	INR	Dose adjustment
Day 3	< 1.3	↑ 10%
	1.3–1.5	No change
	1.6–1.8	↓ 10%
	1.9–2.1	↓ 20%
	2.2–2.5	↓ 50%
	> 2.5	Hold dose for 1 day, then ↓ 50%
Day 5/6	< 1.3	↑ 50%
	1.4–1.7	↑ 20%
	1.8–2.5	No change
	2.6–3.0	↓ 20%
	3.1–3.9	↓ 50%
	≥ 4.0	Hold dose for 1 day, then ↓ 50%
Day 7/8/9	< 1.5	↑ 20%
	1.5–1.9	↑ 10%
	2.0–2.8	No change
	2.9–3.5	↓ 10%
	3.6–4.0	Hold dose for 1 day, then ↓ 15%
	≥ 4.0	Hold dose, test INR daily until in range (2–3), then ↓ 25%

↑ indicates dose increase; ↓ indicates dose decrease.

(Drozda et al., 2015). There are consequently questions regarding the general applicability of regression-based dosing algorithms developed for one population, e.g. Europeans, to be used in others, e.g. non-white patients. Therefore, some investigators have argued that the influence of genetic variants on warfarin dosing requirements could differ by race, and that race-specific regression algorithms should be developed and used to optimally dose warfarin in different ethnic populations (Hernandez et al., 2014; Limdi et al., 2015). This undoubtedly adds another layer of complexity to a drug that is already difficult to dose. Furthermore, since warfarin has a delayed antithrombotic effect until approximately the fifth day of therapy depending on the clearance of the rate-limiting coagulation factor II, current regression-based dosing algorithms fail to account for the dynamic dose/response relationships, which limits their usefulness to guide warfarin dosing during the critical initiation phase (Horton and Bushwick, 1999).

4. Performance of genotype-guided algorithm in ethnically diverse population

In a recent publication, we analyzed data from ethnically diverse patients (57% African Americans, 17% Hispanics, and 14% Whites) who were newly starting warfarin according to dosing algorithm at warfarindosing.org, which provides therapeutic dose estimations for patients based on their genetic and clinical characteristics (Arwood et al., 2016; Nutescu et al., 2013). Our results showed that the percentage of time below, within, and above the therapeutic range differed between patients during the initiation phase based on the number of variant *VKORC1/CYP2C9* alleles (Fig. 2) (Arwood et al., 2016). In particular, we observed that patients with one or more variant alleles were more sensitive to warfarin and responded quicker than wild-type carriers as indicated by the rapid decrease in the % time below therapeutic range during the early phase of therapy. On the other hand, these patients were also at a higher risk of bleeding after the initiation phase, as shown by the spike in their % time above therapeutic range during days 19–25. Our findings are consistent with previous literature reports and indicate that, even in patients undergoing genotype-guided warfarin dosing, patients with variant *VKORC1* and/or *CYP2C9* alleles achieve therapeutic INR levels more rapidly but are also at a higher risk of over-anticoagulation compared to those without a variant (Limdi et al., 2009).

More specifically, simulations performed using the previously published kinetic/pharmacodynamic (K/PD) model by Hamberg et al. (Hamberg et al., 2010) suggested that there were genotype differences in the ability of the coagulation system to respond to adjustments in daily dose. For example, adjustments in daily dose induce a steeper change in INR response in patients with a *CYP2C9* or *VKORC1* -1639A polymorphism compared to those with the *VKORC1* GG and *CYP2C9* *1/*1 genotypes (Fig. 3A and B). The time needed to achieve steady-

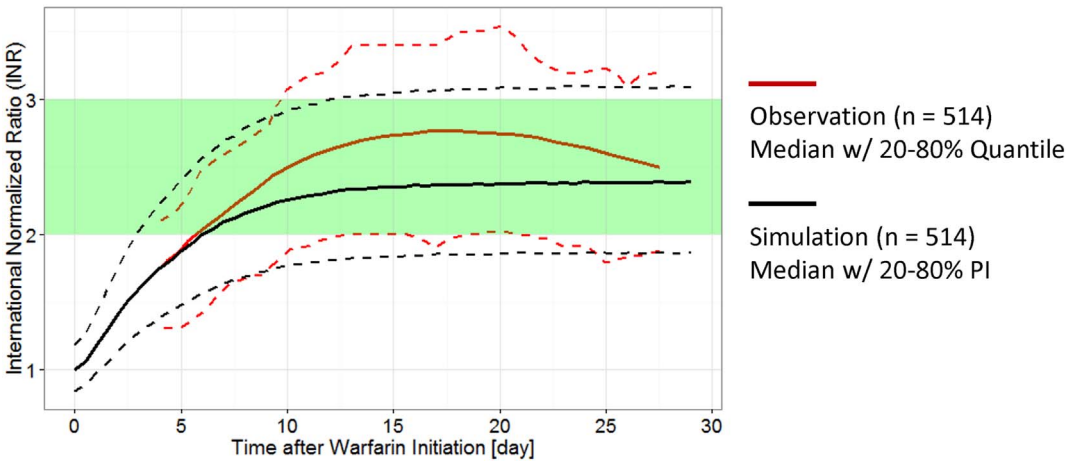

Fig. 4. INR response of genotype-guided group in COAG trial (Kimmel et al., 2013) overlaid with in silico clinical trial simulations (n = 100) in virtual individuals with consistent demographics distributions. Note: green shaded area indicates therapeutic window of INR 2–3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

state (SS) is different across *CYP2C9* genotypes due to the differences in S-warfarin elimination half-lives, whereas the time needed to achieve SS remains the same across *VKORC1* genotypes (Fig. 3C and D). In other words, dose adjustments based on frequent INR monitoring will trigger different responses in patients with different *CYP2C9* and *VKORC1* genotypes.

5. Improving upon current genotype-guided algorithms

As mentioned in the sections above, there were two aspects in which current regression-based dosing algorithms failed to deliver adequate performance. First, genotype-guided dosing was not able to achieve the same level of treatment benefits in non-white populations, possibly because they were developed based on multivariate regression analysis with mostly European/White data and do not include genetic variants found frequently in non-white populations. Second, there are differential genotype effects on drug response during the initiation phase even for patients receiving genotype-guided dosing, which is a problem since current algorithms only estimate a stable therapeutic dose and have limited ability in providing dosing guidance on how to effectively reach therapeutic SS uniformly across genotypes.

In our recent paper in *Clinical Pharmacology & Therapeutics*, we proposed a model-directed dosing nomogram in order to overcome these limitations (Arwood et al., 2016; Hamberg et al., 2010). To develop this nomogram, we leveraged clinical warfarin dose/response data from ethnically diverse patients to inform respective model parameters, which, in combination with literature reported parameters for Europeans (Hamberg et al., 2010), allowed us to predict optimal warfarin dosing regimen across genotypes and ethnicities. Additionally, we used clearance data for *CYP2C9*8* from Liu et al. to extrapolate dose reduction in **8* carriers, since *CYP2C9*8* was identified as an important variant for warfarin dose/response for African Americans (Cavallari et al., 2010; Liu et al., 2012). As shown in Table 1, our optimized dosing nomogram consists of a pharmacogenetics-based loading dose grid on day 1 (depending on combinations of *CYP2C9* and *VKORC1* polymorphisms), a maintenance dose calculation on day 3 (depending on genetic and clinical factors), and dose adjustment directions on days 3, 5/6, 7/8/9 depending on the INR readings. Based on simulations, the utilization of the present dosing nomogram in both ethnically diverse and European populations has the potential to enable safe and effective attainment of therapeutic INR within one week of therapy initiation. Furthermore, the INR response profiles during the critical initiation phase are predicted to be uniform across patients with different *VKORC1* and *CYP2C9* genotype combinations since the underlying model accounts for their differential dose/response behaviors.

6. Further model application: in silico clinical trial simulations

A prospective clinical trial would be necessary to compare the clinical utility of the nomogram versus the standard of care or other dosing algorithms. The design of this trial can be informed via clinical trial simulations, and respective simulated trial outcomes can be explored in order to gain confidence in the proposed dosing regimen and to identify potential unknown sources of variability. In a first attempt to do so, we conducted in silico clinical trial simulations in virtual individuals with consistent clinical and genetic demographics distribution (age, gender, *VKORC1* and *CYP2C9* genotype frequencies, etc.), while implementing the full dosing protocol used in the COAG trial, and compared the resulting simulations to their observed INR response for the genotype-guided group (n = 514) (Kimmel et al., 2013). As shown in Fig. 4, our simulations were in agreement with observed INR response from the genotype-guided group in the COAG trial and could capture INR responses during the initiation phase of therapy reasonably well. The consistency of in silico trial simulations with observations demonstrate the feasibility of using this approach to prospectively refine the proposed dosing nomogram in future trial design.

7. Summary

Because of warfarin's narrow therapeutic index and high inter-individual variability in dose-response, initiating with a fixed dosing approach (e.g. 5 mg/day) may not be an adequate strategy as it neglects the impact of genetic variability on the system's ability to respond to dosing changes. For this reason, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has specifically recommended the use of genotype-guided algorithms developed by IWPC and Gage et al. (warfarindosing.org) to guide warfarin dosing when genotype information is available. However, current algorithms are based on multivariate regression analysis correlating therapeutic warfarin doses with clinical (age, body surface area, etc.) and genotype factors (*VKORC1* and *CYP2C9* polymorphisms) in mostly European/White patients, without accounting for variants important in non-whites. Furthermore, without accounting for the dynamic dose/response relationship, current algorithms are limited in their usefulness to guide warfarin dosing during the critical initiation phase, since the possession of variant *VKORC1* and/or *CYP2C9* polymorphisms has been associated with a more rapid attainment of target INR and higher risk of over-anticoagulation even in genotype-type guided patients (Limdi et al., 2009). To address these shortcomings, we have developed a dynamic dosing nomogram that includes a loading dose, a maintenance dose, and several dose adjustment options during the first week of therapy initiation through novel applications of a previously published K/PD model (Arwood et al., 2016; Hamberg et al., 2010). This approach leverages data from both ethnically diverse and European patients, while accounting for the differential dose/response behaviors due to *VKORC1* and *CYP2C9* genotypes. According to simulations, the utilization of our dosing nomogram could enable effective attainment of therapeutic INR within one week in both ethnically diverse and European populations, with uniform INR response across genotypes. Furthermore, in silico clinical trial simulations using the K/PD model could be a feasible approach to help to further refine our dosing nomogram to be more applicable in the clinical setting and explore possible outcomes even before prospective clinical trials are initiated.

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