Development of a Universal Pharmacogenetics-Guided Warfarin Dosing Nomogram

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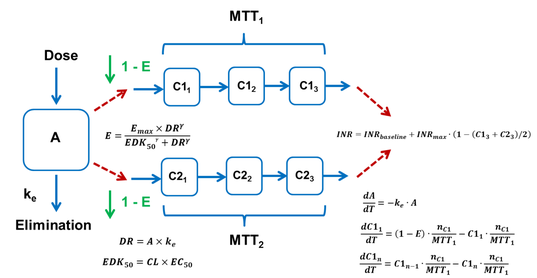
Introduction

Although warfarin is a widely prescribed narrow therapeutic index anticoagulant, suboptimal dosing can cause serious complications including bleeding and thrombosis. Genotype-guided algorithms, such as warfarindosing.org, have been developed to facilitate optimal dosing in patients, for whom genetic information (*VKORC1*, *CYP2C9*, and etc.) is available. However, these regression-based algorithms primarily provide maintenance dose recommendations and are typically developed based on data from Caucasians on stable warfarin dosing. Findings from the COAG (Clarification of Optimal Anticoagulation through Genetics) trial, which was conducted in a diverse population (27% African Americans and 6% Hispanics), suggest that African Americans actually did worse when receiving genotype-guided dosing compared to those receiving standard dosing (1). To overcome these limitations, we developed a dynamic, pharmacogenetics-guided dosing nomogram that can guide optimal warfarin dosing in diverse populations.

Methods

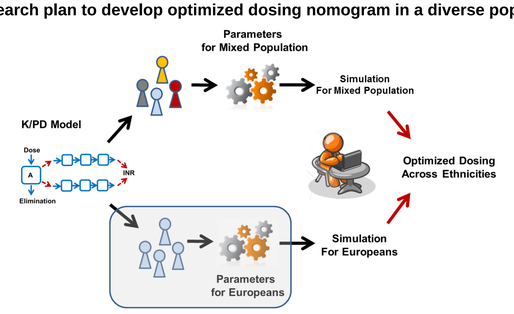
Data from patients of diverse ethnicities (57% African Americans,17% Hispanics, 16% White, and others) initiating warfarin with genotype-guided dosing (warfarindosing.org) were used in this study. Data management and exploratory analysis were performed in R (version 3.2.1). The Rosendaal method was used to calculate time in therapeutic range, assuming linear change between two consecutive INR measurements. A mechanism-based population kinetic-pharmacodynamics (K-PD) model characterizing warfarin dose/response was developed by expanding the model by Hamberg *et al.* (2) in NONMEM® (version 7.3).

Figure 1: Representation diagram for K-PD model of warfarin dose/response relationship



Warfarin initiation nomogram was developed based on simulations in virtual individuals with different covariate combinations. The parameters reported by Hamberg *et al.* (2) and those trained with our own dataset were used to simulate dose/response behavior in European and ethnically diverse populations, respectively.

Figure 2: Research plan to develop optimized dosing nomogram in a diverse population



Results

Table 1: Estimated parameters for the K/PD model based on data from European (Hamberg estimates (2)) and an ethnically diverse population (our estimates)

PK Parameters	Hamberg Estimate (% RSE)	Our Estimate (% RSE)
Structural Model		
CL per *1 allele (L/h)	0.174 (4.48)	Same (FIX)
CL per *2 allele (L/h)	0.0879 (15.0)	
CL per *3 allele (L/h)	0.0422 (46.0)	
Age Effect on CL (% change/year)	-0.571 (57.8)	
V (L)	14.3 (3.45)	
K_a (1/h)	2 (FIX)	
PD Parameters		
Structural Model		
E_{max}	1 (FIX)	1 (FIX)
γ	1.15 (4.4)	1.33 (2)
EC_{50} per *VKORC1* G allele (mg/L)	2.05 (10.2)	1.71 (2)
EC_{50} per *VKORC1* A allele (mg/L)	0.96 (9.7)	0.58 (7)
MTT1 (h)	28.6 (2.4)	49.9 (7)
MTT2 – MTT1 (h)	89.7 (4.6)	44.8 (18)
Interindividual variability		
η_{EC50} (%)	34.0 (6.1)	113 (8)
η_{KDE} (%)	58.9 (17.3)	42.9 (7)
Residual variability		
ε_{INR}	20.0 (1.2)	20.5 (3)

Table 2: A) Pharmacogenetics-based loading dose grid (in milligrams) 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

A)

	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	10	10	10	7.5	7.5	7.5
GA	10	7.5	7.5	5	5	5
AA	3	3	3	3	3	3

B)

$$Maintenance\ Dose\ (mg) = Genetics\text{–}Based\ Dose\ Grid - 0.01 * Age$$

	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	9	7	6.3	4.5	3.6	2.6
GA	6.7	5.2	4.4	3.2	2.7	2
AA	3.2	2.7	2.4	2.1	1.7	1.4

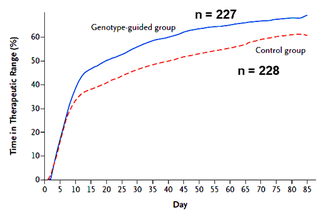
C)

	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%

Results (cont'd)

Figure 3: Percent time in therapeutic INR range of 2-3 during warfarin therapy for (A) Europeans in the EU-PACT Trial (3) and (B) ethnically diverse patients receiving genotype-guided dosing (warfarindosing.org)

A) Homogenous Europeans (EU-PACT Trial)



B) UI-Health patients receiving genotype-guided dosing (57% AA, 17% Hispanics, 16% White, etc.)

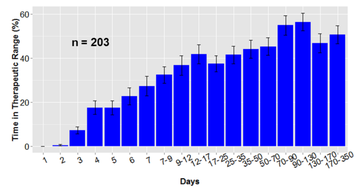


Figure 4: Simulated INR profiles in virtual individuals with different combinations of covariates, such as *VKORC1* and *CYP2C9*, who were dosed according to our optimized warfarin dosing nomogram. INR simulations for A, B) an ethnically diverse population and D, E) for a European population

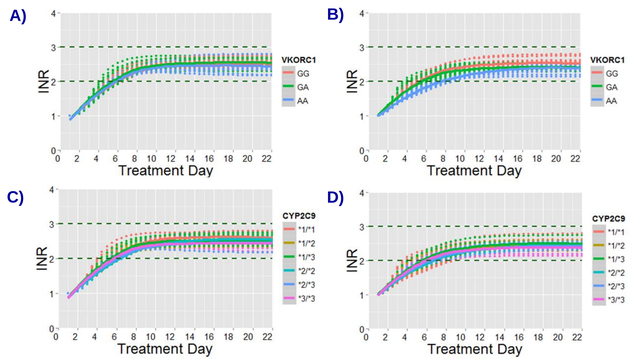
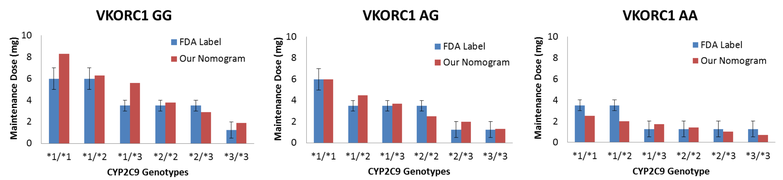


Figure 5: Comparison of warfarin maintenance doses for a 70-year old individual calculated using our nomogram vs. dose recommendations shown on the FDA label for Coumadin® (27). Error bar indicates FDA recommended dose range



Conclusions

- Exploratory analysis indicates that our patients spent less time in therapeutic range compared to Europeans in the EU-PACT trial (55% vs. 65%) at 70-90 days of therapy.
- We developed a dynamic dosing nomogram that could enable patients to reach therapeutic INR within 1 week and remain stable across genotypes and ethnicities.
- Our nomogram was developed using data from patients newly starting warfarin and could make more accurate loading dose predictions.
- Our maintenance doses were consistent with FDA dose recommendations across different combinations of *VKORC1* and *CYP2C9*.

References

1. Kimmel et al., N Engl J Med 369: 2283-2293 (2013)
2. Hamberg et al., Clin Pharmacol Ther 87: 727-34 (2010)
3. Pirmohamed et al., N Engl J Med 369: 2294-303 (2013)
4. COUMADIN® (Warfarin Sodium) package insert