Clinical Implementation Of Warfarin Pharmacogenetics In A Real-world Setting: A Proposal For A New Pharmacogenetic Dosing Approach For Diverse Patient Populations

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BACKGROUND

- Warfarin remains frequently prescribed despite the availability of direct oral anticoagulants
- Attaining therapeutic anticoagulation efficiently with warfarin is important to reduce thrombotic/bleeding risks and is influenced by genotype
  - Pharmacogenetic dosing algorithms may improve attainment of therapeutic anticoagulation
  - Yet current algorithms are based on stable warfarin dose data

OBJECTIVES

- To compare anticoagulation-related endpoints by genotype group among patients receiving genotype-guided dosing with the use of recommended pharmacogenetic dosing algorithms in a real-world setting
- To derive a novel dosing nomogram to more optimally dose warfarin

METHODS

Study population and procedures:

- Adult patients newly starting warfarin received *VKORC1* and *CYP2C9* genotype-guided dosing by the University of Illinois Hospital and Health Sciences System (UI Health) Personalized Medicine Program (PMP) as part of clinical care
  - Dose recommendations were calculated via algorithms available through www.warfarindosing.org
- Exclusion criteria:
  - History of warfarin use in previous 6 months
  - History of liver transplant
  - INR goal other than 2-3

Data collection and statistical analysis:

- Medical record review of patients who provided written informed consent
- Anticoagulation-related metrics in the initial 28 days of therapy were compared among patients with 0, 1, or ≥2 reduced-function (RF) *VKORC1*-1639A and/or *CYP2C9*2, *3, *5, *6, *11 or *14* alleles
  - Time to first therapeutic INR and rate of INR increase: multiple linear regression, adjusted for race and inpatient status
  - Percentage of patients with INR >4: χ^2 test or Fisher's exact test
  - Daily inpatient warfarin dose (mg): one-way analysis of variance (ANOVA)
  - The percentage of time above, below, and within therapeutic INR range (2–3): calculated in R (v. 3.2.1) using the Rosendaal method
- Generated Kaplan-Meier plot; significance tested using Wilcoxon test of equality over strata
- Performed piecewise Cox proportional hazards regression

Development of warfarin initiation nomogram:

- A population kinetic/pharmacodynamic model was developed to characterize the warfarin dose/response relationship
  - Used in clinical trial simulations to create a dosing nomogram

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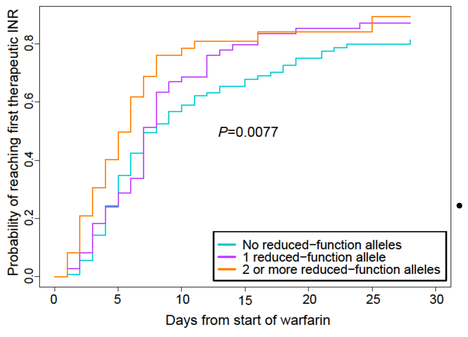
RESULTS

Table 1. Baseline characteristics by genetic subgroups

Baseline Characteristics	Genetic subgroup			P-value†
	No variants (n=133)	1 variant (n=75)	≥2 variants (n=49)	
Age (years), mean ± SD	51 ± 15	50 ± 17	53 ± 16	0.61
Female sex, %	49.6	48.0	51.0	0.95
BSA (m^2), mean ± SD	2.1 ± 0.4	2.0 ± 0.4	2.0 ± 0.3	0.22
Baseline INR, mean ± SD	1.2 ± 0.1	1.2 ± 0.2	1.2 ± 0.1	0.95
Self-reported race/ethnicity, %				
African American	77.4	38.7	20.4	<0.0001
Non-Hispanic Caucasian	8.3	20.0	28.6	
Hispanic Caucasian	6.8	28.0	28.6	
Other	7.6	13.3	22.5	
Warfarin indication, %				
VTE	66.9	57.3	57.1	0.28
Atrial fibrillation	16.5	22.7	20.4	0.54
Atrial or ventricular thrombus	5.3	2.7	4.1	0.72
Cardioembolic stroke	2.3	6.7	2.0	0.22
Cerebral venous thrombosis	3.0	1.3	8.2	0.15
Other	6.0	9.3	8.2	0.63
Setting of first therapeutic INR (n=173)				
Inpatient, %	65.1	52.8	62.2	0.36
Outpatient, %	34.9	47.2	37.8	

INR – international normalized ratio; SD – standard deviation; VTE – venous thromboembolism
† *P*-values were generated from χ^2 test of independence or ANOVA in order to assess differences among the 3 genetic subgroups (0, 1, or ≥2 reduced-function alleles)

Figure 1. Kaplan-Meier time-to-therapeutic INR estimates for patients with 0, 1, or ≥2 RF alleles



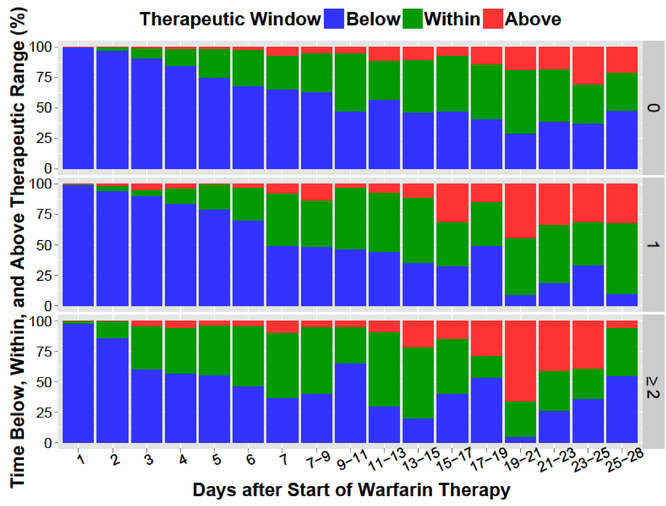
- Adjusting for race and inpatient status, there was an increased chance of achieving first therapeutic INR at any time between days 0 and 10 with each additional RF allele (HR 1.44, 95% CI 1.14–1.81, *P*=0.0019)
- There was no significant association between genetic subgroup and achieving first therapeutic INR between days 11 and 28 (HR 0.99, 95% CI 0.59–1.64, *P*=0.9524)

Table 2. Anticoagulation metrics by genetic subgroups

Metrics	Number of variant alleles (*VKORC1*-1639G>A or *CYP2C9*)			P-value
	0	1	≥2	
Time to first therapeutic INR (days), mean ± SD	(n=83) 7.8 ± 5.8	(n=53) 7.2 ± 4.7	(n=37) 5.4 ± 4.6	0.0004
Rate of INR increase, mean ± SD	(n=83) 0.21 ± 0.16	(n=53) 0.23 ± 0.19	(n=37) 0.38 ± 0.31	<0.0001
Patients with an INR >4, %	(n=133) 5.3	(n=75) 10.7	(n=49) 14.3	0.1151
Daily warfarin dose during hospitalization (in mg), mean ± SD	(n=133) 6.3 ± 2.5	(n=75) 5.2 ± 1.9	(n=49) 3.9 ± 1.9	<0.0001

- For patients with 0, 1, and ≥2 RF alleles, mean percentage of time in therapeutic range in the first 28 days was 22.2, 27.8, and 32.2% (*P*=0.0127), respectively
- Mean percentage of time below therapeutic range was 72.1, 61.1, and 57.0% (*P*=0.0016), respectively
- Patients with ≥1 RF alleles were more likely to have an INR >3 in the later phase (days 11–28) than those without variant alleles (*P*=0.0178)

Figure 2. Percentage of time in INR range (as calculated by Rosendaal method) that is i) below 2 (blue), ii) within 2-3 (green), and iii) above 3 (red) for patients with 0, 1, and ≥2 variant alleles



- In simulations, warfarin dosing with our new nomogram that included genotype-specific loading doses reduced time to first therapeutic INR for patients with 0-1 RF alleles from 7.6 ± 5.4 to 4.2 ± 0.6 days (*P*=0.001)

CONCLUSIONS

- Our data suggest that more aggressive dosing than recommended by current pharmacogenetic dosing algorithms is needed for patients with 0-1 RF *VKORC1* or *CYP2C9* alleles, which encompasses most African American and Caucasian patients, while more cautious dosing may be necessary to avoid over-anticoagulation in multiple variant allele carriers
- Our novel dosing nomogram, which provides genotype-specific loading dose recommendations, may enable more effective attainment of therapeutic anticoagulation among genotype groups within the diverse populations found in the US

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