CLINICAL & EXPERIMENTAL
THROMBOSIS AND HEMOSTASIS

Original Article

Clin Exp Thromb Hemost 2020;6(1):6-11
http://dx.doi.org/10.14345/ceth.20002

The Algorithm with Multiple Genotypes on Optimal Warfarin Doses in Korean Patients

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Received: 21 April 2020
Accepted: 9 May 2020

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Dr. MH Kim received a research grant from Bayer co. Other authors did not have any conflict.

Background and Objectives: Genetic factors that affect warfarin dose are not routinely evaluated in the Korean population. In this study, we investigated the influence of genetic polymorphisms (GPs) on optimal warfarin dose (OWD) and derived an OWD prediction algorithm based on Korean patients with various diseases requiring anticoagulation therapy.
Methods: One hundred eight patients taking warfarin were included. We evaluated clinical characteristics, OWD, international normalized ratio (INR), VKORC1, CYP2C9, and CYP4F2 polymorphisms, as well as medication information. OWD was defined as the maintenance dose that kept a patient's INR within the target range based on at least two consecutive laboratory measurements separated by more one 1 week.
Results: The 108 patients (mean age: 61.5±12.4 yr, 48% male) had a mean OWD of 3.12±1.30 (1-9) mg/day. VKORC1 wild-type patients (AA) had a lower OWD than VKORC1 variant patients (GA). Significantly more OWD patients had the CYP2C9 wild-type genotype than CYP2C9 mutant genotypes. Among the three genotypes of CYP4F2, two carriers had a significantly higher OWD than patients who had the wild-type genotype. We derived an OWD algorithm that included VKORC1, CYP2C9, CYP4F2, body mass index (BMI), age, amiodarone use, and diuretic use.
Conclusion: Our algorithm was capable of explaining 41.8% of the total variation in warfarin dose in our patient cohort. Multiple GPs affect the OWD in Korean patients.

Keywords: algorithm, optimal warfarin dose, VKORC1, CYP2C9, CYP4F2

Introduction

Warfarin is widely prescribed to prevent and treat thromboembolic diseases such as atrial fibrillation (AF), deep vein thrombosis (DVT), and pulmonary thromboembolic disease (PTE).[1] However, multiple challenges making it difficult to determine the optimal dose of warfarin including the long half-life of warfarin, numerous foods that interfere with the actions of warfarin, and drug interactions.[2] To ensure a suitable level of anticoagulation, prothrombin time (PT) standardized by the international normalized ratio (INR) should be monitored closely.

Cytochrome P-450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) genetic polymorphisms (GPs) affect warfarin pharmacodynamics,[3] and the product label of warfarin encourages genotype-guided dosing.[4] Warfarin is a mixture of R- and S-warfarin. S-warfarin is about 3- to 5-fold more effective than R-warfarin at anticoagulation. CYP2C9 is the main enzyme that metabolizes S-warfarin. Active drug can be biotransformed by the CYP2C9 isoenzyme to an inactive metabolite, and the presence of loss-of-function polymorphisms leads to a higher active drug concentration. Therefore, CYP2C9 polymorphisms affect warfarin dose.[3] VKORC1 is a warfarin-sensitive and rate-limiting enzyme. Warfarin exerts its anticoagulant effects by inhibiting VKORC1 to affect vitamin K circulation. A common VKORC1 variant (1639G>A) has decreased gene expression. Consequently, patients with this VKORC1 variant have different warfarin dose requirements than patients with wild-type VKORC1.[5] GPs in CYP2C9 and VKORC1 combined with non-genetic factors were able to explain 45% of the variance in individual warfarin dose in Chinese patients,[6] but 55% of the variance remained unexplained. Cytochrome P-450 4F2 (CYP4F2) is a vitamin K1 oxidase that affects warfarin dose. Adding this factor could account for more of the variation among patients in optimal warfarin dose, but the effect of CYP4F2 on warfarin dose is controversial as although one study found that CYP4F2 genotype significantly affected warfarin dose,[7] other studied reported the opposite.[8,9]

Ethnic differences have a large influence on OWD. Asian patients have lower warfarin dose requirements than patients of other ethnicities.[10] Warfarin dose prediction algorithms that were derived based on patients of other ethnicities may therefore not be suitable for Korean patients. Our aim in this study was to determine the effects of

various GPs on OWD in Korean patients and derive a warfarin dose prediction algorithm for Korean patients. To improve the overall predictability of our algorithm, we included the CYP4F2 gene in our algorithm.

Methods

Study design

One hundred eight Korean patients taking warfarin were enrolled in the this study from July 2007 to June 2018. Inclusion criteria were patients who were between 20-80 years old with a body weight above 50 kg taking warfarin. Exclusion criteria were a history of chronic liver failure, use of other anticoagulant medications, active malignancy, renal disease (creatinine >2.0 mg/dL or eGFR <45 mL/min), or life expectancy <1 year.

All patients provided written informed consent prior to participating in the study. We collected clinical data by reviewing patients' charts and electronic medical records, from outpatient clinic visits, as well as by telephone. Data included sex, age, height, body weight, smoking, alcohol, target INR, comorbidities, concurrent medications, left ventricular ejection fraction (LVEF), and OWD. Main indications for treatment were atrial fibrillation (AF), DVT/PTE, and heart valve disease (HVD). Comorbidities were cerebral infarction (CI), congestive heart failure (CHF), hypertension, diabetes mellitus (DM), and hyperlipidemia (HLP). Concurrent medications were β-blockers, amiodarone, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEi), aspirin, clopidogrel, statins, calcium channel blockers (CCBs), diuretics, and nitrates. The concomitant medications were included when the patients were continuously taking these for at least 7 days during treatment. OWD was defined as the maintenance dose for which a patient's INR was within the target range (INR of 2-3) on ≥2 consecutive laboratory measurements separated by at least 1 week.[11] We used fixed dosing experience-based practices in the trial. Initial and subsequent warfarin doses were determined empirically by the physicians.

Genotyping

Genomic DNA of patients was isolated from peripheral whole blood using the QIAamp Blood Mini Kit (QIAGEN, Hilden, Germany) according to standard procedures recommended by the manufacturer, and stored at -20°C until use. CYP2C9*3 (42614A>C, rs1057910), VKORC1 (1639G>A, rs9923231), and CYP4F2 (18000G>A, rs2108622) polymorphisms were detected by polymerase chain reaction (PCR). Multiplex PCR conditions were optimized for SNaPshot reaction. PCR amplification was carried out in a total volume of 30 μL containing 100 ng of genomic DNA, 3 μL of 10X PCR buffer containing Mg^{2+}, 250 μM of each dNTP, 0.13 μM of each primer, and 5 U/μL of rTaq DNA polymerase (TaKaRa, Shiga, Japan). Cycling was performed using the GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA, USA) and standard methods.[12] SNaPshot Multiplex Kit (Applied Biosystems, CA, USA) was used for single nucleotide polymorphism (SNP) genotyping. Then samples were analyzed using an ABI-Prism 3130 genetic analyzer (Applied Biosystems, CA, USA). SNaPshot results were analyzed using GeneMapper® version 3.7 software (Applied Biosystems, CA, USA). Genotype classifications were as follow: VKORC1 AA and VKORC1 GA, CYP2C9*1/*1 and CYP2C9*1/*3, CYP4F2 GG and CYP4F2 GA and CYP4F2 AA. We did not find VKORC1 GG and CYP2C9*3/*3 genotypes in this cohort of Korean patients.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are presented as means±standard deviations. The independent t-test was used to determine the associations between GP and OWD. A generalized linear model (GLM) was used to analyze differences in OWD according to CYP2C9, VKORC1, or CYP4F2 polymorphisms. When analyzing the GLM, we adjusted the baseline characteristics and estimated the mean (standard error). Univariate analyses and multiple linear regression were performed to investigate the relationships of warfarin dose to other variables and to develop the algorithm. In this statistical modeling, the stepwise selection method was applied to identify significant clinical covari-

Table 1. Baseline characteristics of the study population

Total (n=108)	Numbers of patients (%)
Female	56 (52)
Age (yr)	
<60	46 (42)
60-70	58 (54)
>70	4 (4)
BMI (kg/m²)	
<18.5	5 (5)
18.5-23	34 (31)
>23	69 (64)
Smoking	11 (10)
Alcohol	12 (11)
LVEF (%)	
≥50	78 (72)
<50	25 (22)
Main indications for treatment	
AF	83 (77)
PTE/DVT	14 (13)
Heart valve disease	36 (33)
Comorbidities	
Cerebral infarction	20 (19)
Congestive heart failure	34 (31)
Hypertension	36 (33)
Diabetic mellitus	15 (14)
Hyperlipidemia	6 (6)
Medications	
β-blockers	13 (12)
Amiodarone	32 (30)
ARBs	20 (19)
ACEi	10 (9)
Aspirin	16 (15)
Clopidogrel	17 (16)
Statins	23 (21)
CCBs	20 (19)
Diuretics	74 (69)
Nitrates	7 (6)

Values are presented as numbers (%).
BMI, body mass index; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; PTE, pulmonary thromboembolic disease; DVT, deep vein thrombosis; ARBs, angiotensin receptor blockers; ACEi, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

Table 2. Daily stable warfarin dose of the study patients

Total (n=108)	Warfarin dose (mg/day)	*P*-value
Sex		
Female	3.1±1.5	0.703
Male	3.2±1.1	
Age (yr)		
<60	3.6±1.6	0.001
60-70	2.8±0.9	
>70	2.7±0.6	
BMI (kg/m²)		
<18.5	2.4±1.1	0.058
18.5-23	2.8±1.0	
>23	3.3±1.4	
Smoking		
Yes	3.1±1.1	0.971
No	3.1±1.3	
Alcohol		
Yes	3.2±1.2	0.887
No	3.1±1.3	
LVEF (%)		
≥50	3.2±1.4	0.059
<50	2.7±1.0	
Main indications for treatment		
AF		
Present	2.9±1.2	0.006
Absent	3.7±1.4	
PTE/DVT		
Present	3.3±1.2	0.529
Absent	3.1±1.3	
Heart valve disease		
Present	3.5±1.3	0.060
Absent	3.0±1.3	
Comorbidities		
Cerebral infarction		
Present	2.9±1.1	0.314
Absent	3.2±1.3	
Congestive heart failure		
Present	2.7±1.1	0.319
Absent	3.3±1.3	
Hypertension		
Present	3.1±0.9	0.926
Absent	3.1±1.5	
Diabetic mellitus		
Present	3.1±1.8	0.917
Absent	3.1±1.2	
Hyperlipidemia		
Present	3.5±1.2	0.413
Absent	3.1±1.3	
Medications		
β-blockers		
Yes	3.0±1.1	0.777
No	3.1±1.3	
Amiodarone		
Yes	2.6±1.1	0.012
No	3.3±1.3	
ARBs		
Yes	3.3±1.1	0.548
No	3.1±1.3	
ACEi		
Yes	3.0±1.2	0.769
No	3.1±1.3	
Aspirin		
Yes	3.1±1.1	0.983
No	3.1±1.3	
Clopidogrel		
Yes	3.0±1.2	0.729
No	3.1±1.3	
Statins		
Yes	3.0±1.2	0.617
No	3.1±1.3	
CCBs		
Yes	3.0±1.2	0.735
No	3.1±1.3	
Diuretics		
Yes	2.9±1.2	0.026
No	3.5±1.4	
Nitrates		
Yes	3.9±0.9	0.103
No	3.1±1.3	

Values are presented as means±standard deviations.
BMI, body mass index; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; PTE, pulmonary thromboembolic disease; DVT, deep vein thrombosis; ARBs, angiotensin receptor blockers; ACEi, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

ates. SPSS software 20.0 (SPSS, Inc, Chicago, IL, USA) was used for all statistical analyses. *P*-value<0.05 was considered to be statistically significant.

Results

Clinical characteristics

As shown in Table 1, the average age of patients was 61.5±12.4 yr, and 48% of patients were men. Only 4% of patients were older than 70 years. Most patients (69, 64%) had a high body mass index (BMI >23). Main indications for warfarin treatment were AF (77%), PTE/DVT (13%), and HVD (33%). Comorbidities were CI (19%), CHF (31%), hypertension (33%), DM (14%), and HLP (6%). Only thirty-two (30%) patients reported receiving amiodarone. More patients (74, 69%) were treated with diuretics. The average OWD was 3.12±1.30 (1-9) mg/day. The average time percentage in the therapeutic range (TTR) in the trial was 56%. Older patients (>70 years) required a significantly higher OWD (P=0.001). Patients diagnosed with AF, those treated with amiodarone, and those treated with diuretics had a significantly lower OWD than other patients (P=0.006, P=0.012, P=0.026, respectively). No other clinical characteristics

Table 3. Genotype frequencies of VKORC1, CYP2C9, and CYP4F2

Gene	SNP	Allele	Patients, No. (%)	Genotype	Patients, No. (%)
VKORC1	1639G>A	A	205 (94.9)	AA	97 (89.8)
	(rs9923231)	G	11 (5.1)	GA	11 (10.2)
CYP2C9	42614A>C	*1	205 (94.9)	*1/*1	97 (89.8)
	(rs1057910)	*3	11 (5.1)	*1/*3	11 (10.2)
CYP4F2	18000 G>A	G	147 (68.1)	GG	47 (43.5)
	(rs2108622)	A	69 (31.9)	GA	53 (49.1)
				AA	8 (7.4)

Values are presented as numbers (%).
SNP, single nucleotide polymorphism.

had a statistically significant effect on daily stable warfarin dose (Table 2).

Genotype frequencies of VKORC1, CYP2C9 and CYP4F2

Ninety-seven patients (89.8%) were homozygous for the wild-type A allele of VKORC1, 11 patients (10.2%) were heterozygous for the wild-type A allele, and no patients were homozygous for the variant G allele. Ninety-seven patients (89.8%) were homozygous for CYP2C9*1 and 11 patients (10.2%) were heterozygous for CYP2C9*3; no *3/*3 genotypes were observed. CYP4F2 allele frequencies were 68.1% for the G allele and 31.9% for the A allele (Table 3).

Effects of GPs on OWD

Figure 1 summarizes the effects of GPs on OWD. VKORC1 wild-type patients (AA) had a lower OWD than variant patients (GA) (2.95 vs 4.63 mg/day, respectively, $P<0.001$). The average OWD of patients who were CYP2C9*1/*1 was significantly higher than that of patients who were CYP2C9*1/*3 (3.30 vs 1.65 mg/day, respectively, $P<0.001$). Mean OWD was significantly higher in patients with the CYP4F2 AA genotype than those with the GA or GG genotypes (4.40 vs. 3.12 vs 2.91 mg/day, respectively, $P=0.014$).

OWD model derivation

We first used single linear recursive analysis, including OWD as the dependent variable and gender, age, BMI, habits, concomitant diseases, combined medications, LVEF, and the three genotypes as potential factors to determine the correlation between these factors and OWD. We developed an OWD prediction algorithm by including factors with a P value below 0.05 in univariate analysis in multiple linear regression analysis. Multivariate analysis including seven variables with $P<0.05$ from univariate analysis (age, BMI, amiodarone, diuretics, VKORC1, CYP2C9 and CYP4F2 genotypes) was performed (Table 4, Table 5). Our model explained 41.8% of warfarin maintenance dose variability.

The equation we derived is

OWD (mg/day)= 4.165+1.500×VKORC1 (GA)-1.115×CYP2C9 (*1/*3)-0.672×CYP4F2 (GG) -0.791×CYP4F2 (GA)-0.993×Age (60-70)-0.810×Age (>70)+0.351 * BMI (18.5-23)+0.656×BMI (>23)-0.400×Amiodarone-0.382×Diuretics.

Coding was as follows: VKORC1 GA=1 if the VKORC1 genotype was GA, otherwise 0; CYP2C9 *1/*3=1 if the CYP2C9 genotype was *1/*3, otherwise 0; CYP4F2 GG=1 if the CYP4F2 genotype was GG, otherwise 0; CYP4F2 GA=1 if the CYP4F2 genotype was GA, otherwise 0; age in decades=1 for 60-70 years, otherwise 0; age in decades=1 for >70 years, otherwise 0; BMI value=1 for: 18.5-23 kg/m², otherwise 0; BMI value=1 for: 23 kg/m², otherwise 0; amiodarone status=1 if patient taking amiodarone, otherwise 0; diuretics status=1 if patient taking diuretics, otherwise 0.

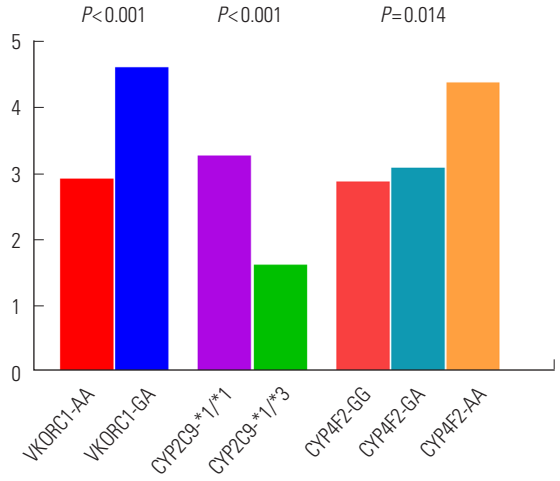

Fig. 1. Genetic polymorphisms influencing warfarin dose.

Discussion

The main contribution of this study was to derive an algorithm to predict OWD in Korean patients with various diseases requiring anticoagulation therapy. This algorithm was able to explain 41.8% of variation in the warfarin dose among the Korean patients enrolled in this study. We also established a definite link between multiple GPs and OWD. We demonstrated that the required dose of warfarin in Korean patients with the wild-type VKORC1 genotype (AA) was lower than that required in patients with the variant (GA) genotype (2.95 vs. 4.63 mg/day). CYP2C9*1/*1-carriers had a significantly higher OWD than CYP2C9*1/*3-carriers (3.30 vs. 1.65 mg/day). Although some researchers observed no significant associations between CYP4F2 polymorphisms and warfarin dose requirement in Korean and Indian patient cohorts,[8,9] we found that Korean CYP4F2 AA-carriers required the highest average OWD compared to GA- or GG-carriers (4.40 vs. 3.12 vs. 2.91 mg/day, respectively, $P=0.014$).

It is well known that ethnicity affects OWD because of genetic variation among different ethnic populations. For example, African–Americans require a higher warfarin dose than other ethnic groups.[13] Warfarin maintenance dose in Asian patients is approximately 30–40% less than that required for Caucasian patients for a similar degree of anticoagulation. These differences have partly been attributed to genetic differences in CYP2C9 and VKORC1.[10] Therefore, algorithms to predict OWD that were developed in other ethnicities may not be suitable for Korean populations. A study showed that adding CYP4F2 to a model to predict warfarin dose increased the R^2 value by 0.9% after adjusting for clinical and genetic variables.[14] We therefore included the CYP4F2 gene in our warfarin pharmacogenetic dose prediction algorithm for Korean patients.

In a previous study that derived an algorithm to predict warfarin maintenance dose in Korean patients with AF, variables included were age, body surface area (BSA), statin status, and genetic factors (VKORC1 and CYP2C9). However, the CYP4F2 genotype was not

Table 4. Univariate factors affecting warfarin dose

Variables	Univariate							
	B	SE	ß	*P*-value	R^2	Adjusted R^2	F-value	*P*-value
Age (ref = <60 yr)								
60-70	-1.064	0.268	-0.381	0.000	0.151	0.135	9.329	0.048
>70	-0.817	0.273	-0.288	0.003				
BMI (ref = <18.5 kg/m²)								
18.5-23	0.822	0.672	0.297	0.224	0.061	0.044	3.439	0.036
>23	1.330	0.655	0.493	0.045				
Gender (ref = female)	0.096	0.252	0.037	0.703	0.001	-0.008	0.146	0.703
Smoking	-0.015	0.416	-0.004	0.971	0.000	-0.009	0.001	0.971
Alcohol	0.057	0.401	0.014	0.887	0.000	-0.009	0.020	0.887
VKORC1 (ref = AA)	1.465	0.391	0.342	<0.001	0.117	0.109	14.027	<0.001
CYP2C9 (ref = *1/*1)	-1.344	0.395	-0.314	0.001	0.098	0.090	11.557	0.001
CYP4F2 (ref = AA)								
GG	-1.220	0.488	-0.467	0.014	0.056	0.038	3.120	0.000
GA	-1.038	0.484	-0.400	0.034				
Main indications for treatment								
PTE/DVT	0.236	0.374	0.061	0.529	0.004	-0.006	0.398	0.529
Heart valvular disease	0.511	0.263	0.186	0.055	0.035	0.025	3.760	0.055
Comorbidities								
Cerebral infarction	-0.326	0.323	-0.098	0.314	0.010	0.000	1.024	0.314
Congestive heart failure	-0.588	0.265	-0.211	0.290	0.011	0.001	4.920	0.290
Hypertension	0.025	0.267	0.009	0.926	0.000	-0.009	0.009	0.926
Diabetic mellitus	-0.038	0.364	-0.010	0.917	0.000	-0.009	0.011	0.917
Hyperlipidemia	0.451	0.548	0.080	0.413	0.006	-0.003	0.677	0.413
Medications								
Amiodarone	-0.687	0.268	-0.242	0.012	0.059	0.050	6.587	0.012
Diuretics	-0.599	0.265	-0.215	0.026	0.046	0.037	5.121	0.026
β-blockers	-0.110	0.387	-0.028	0.777	0.001	-0.009	0.081	0.777
ARBs	0.195	0.324	0.058	0.548	0.003	-0.006	0.364	0.548
ACEi	-0.128	0.434	-0.029	0.769	0.001	-0.009	0.087	0.769
Aspirin	-0.008	0.354	-0.002	0.983	0.000	-0.009	0.000	-0.983
Clopidogrel	-0.120	0.346	-0.034	0.729	0.001	-0.008	0.121	0.729
Statins	-0.154	0.307	0.049	0.617	0.002	-0.007	0.252	0.617
CCBs	-0.110	0.324	-0.033	0.735	0.001	-0.008	0.116	0.735
Nitrates	0.831	0.505	0.158	0.103	0.025	0.016	2.706	0.103

Values are presented as numbers.
BMI, body mass index; PTE, pulmonary thromboembolic disease; DVT, deep vein thrombosis; ARBs, angiotensin receptor blockers; ACEi, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

included.[15] In another study of Korean patients, a multiple regression model that included age, gender, BSA, INR, VKORC1, CYP2C9, CYP4F2, and GGCX polymorphisms explained 35% of the total variation in warfarin dose;[8] however, no co-medication information was included in the algorithm. Lee et al. suggested that CYP4F2, VKORC1, and CYP2C9 are predictive of stable warfarin doses in Korean patients with prosthetic heart valves. Their predictive algorithm included age, VKORC1, and CYP2C9 and explained 35.1% of the variability in warfarin dose. Addition of the CYP4F2 polymorphism increased the R^2 value to 38.0% for stable dose requirements.[16] A multivariate analysis including non-genetic variables (age, AF) and genetic variables (genotypes of VKORC1 rs9934438, CYP2C9 rs1057910, CYP4F2 rs2108622, and UGT rs887829) explained 45.1% of the overall inter-individual variability in warfarin dose requirements in Korean patients with mechanical cardiac valves (MCV). VKORC1 genotypes accounted for 28.2% of the total variation in warfarin dose, CYP2C9 genotypes for 6.6%, age for 3.0%, and CYP4F2 genotypes for 1.8%.[17] In another study, an algorithm that included VKORC1, CYP2C9, CYP4F2, and vitamin D receptor (VDR) genotypes in addition to non-genetic variables explained 47.5% of the variability in stable warfarin dose in Korean patients with MCV, and CYP4F2 explained 1.7% of inter-individual difference in overall warfarin dose.[18] In our study, seven variables including age, BMI, amiodarone use, diuretic use, VKORC1, CYP2C9, and CYP4F2 polymorphisms explained 41.8% of the variance in OWD in Koreans with various diseases requiring anticoagulation therapy.

One clinical trial found that a genotype-guided dosing strategy

Table 5. Multivariate factors affect warfarin dose

Variables	Multivariate			
	B	SE	β	*P*-value
Interceptor	4.165	0.694		0.000
Age (ref = <60 yr)				
60-70	-0.993	0.226	-0.356	0.000
>70	-0.810	0.228	-0.285	0.001
BMI (ref = <18.5 kg/m²)				
18.5-23	0.351	0.549	0.127	0.524
>23	0.656	0.540	0.243	0.227
Diuretics	-0.382	0.215	-0.135	0.079
Amiodarone	-0.400	0.216	-0.143	0.067
VKORC1 (ref = AA)	1.500	0.326	0.350	0.000
CYP2C9 (ref = *1/*1)	-1.115	0.326	-0.260	0.001
CYP4F2 (ref = AA)				
GG	-0.672	0.391	-0.257	0.089
GA	-0.791	0.384	-0.305	0.042
R^2	0.472			
Adjusted R^2	0.418			
F-value	8.673			
P-value	<0.001			
Durbin-Watson	2.001			

Values are presented as numbers.
BMI, body mass index.

did not result in better outcomes than clinically-guided dosing.[19] However, other researchers have reported that a genotype-guided algorithm reduced adverse events, increased anticoagulation control benefits, predicted a stable therapeutic warfarin dose, led to fewer dose adjustments, and improved accuracy and efficiency during the treatment period.[20,21] We confirmed in the current study that including CYP4F2 genotype in our algorithm improved its predictive accuracy in Korean patients with a variety of diseases.

Our study had several limitations. It was conducted based on data collected exclusively from Koreans, and it was a single-center study. Our sample size was also comparatively small. Our goal in the future is to collect more patient-related information to validate the effectiveness of our algorithm and determine other factors that may affect OWD in Korean patients (such as polymorphisms in the gamma-glutamyl carboxylase gene).

In conclusion, our algorithm was able to explain 41.8% of warfarin dose differences in Korean patients with various diseases requiring anticoagulation therapy. VKORC1, CYP2C9, and CYP4F2 GPs all affected OWD in Korean patients. Although CYP4F2 polymorphisms only appear to have a mild influence on OWD, including this gene in an algorithm can improve the ability of the algorithm to accurately predict OWD.

Acknowledgments

This research was supported by Dong-A Unversity Research Fund.

Conflicts of interest

Dr. MH Kim received a research grant from Bayer Co. None of the other authors have conflicts of interest to report.

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