

The Frequency of *CYP2C9*, *VKORC1*, and *CYP4F2* Polymorphisms in Russian Patients With High Thrombotic Risk

Dmitriy Ivashchenko¹, Ilya Rusin¹, Dmitriy Sychev², Andrey Grachev³

¹I. M. Sechenov First Moscow State Medical University,

²Russian Medical Academy of Postgraduate Education, ³SM-Clinic, Russia

Key Words: *CYP2C9*; *VKORC1*; *CYP4F2*; pharmacogenomics; warfarin.

Summary. Background and Objective. *VKORC1*, *CYP2C9*, and *CYP4F2* are known to be responsible for the metabolism of warfarin. The aim was to explore the frequencies of these genotypes in the Russian population and compare the results with those for other populations.

Material and Methods. In total, 91 Caucasian subjects with a mean age of 66.17 years (SD, 10.9) were recruited into the study. Of them, 40 patients (48.2%) were men. In order to obtain necessary clinical data, the medical records of the patients were reviewed. Blood (5 mL) was taken from each subject, and DNA was isolated and used for identification of the *CYP2C9* allele *1, *2, *3, –1639G/A *VKORC1*, and *CYP4F2* V433M rs2108622 C>T, using the real-time polymerase chain reaction–restriction fragment length polymorphism assay.

Results. The *CYP2C9**1/*1 genotype was detected in 67.0%, *CYP2C9**1/*2 in 9.9%, *CYP2C9**1/*3 in 11.0%, *CYP2C9**2/*2 in 2.2%, *CYP2C9**2/*3 in 8.8%, and *CYP2C9**3/*3 in 1.1% of the patients. The results for *VKORC1* were as follows: 49.5% (GG), 28.6% (GA), and 22.0% (AA); meanwhile, those for the genotype *CYP4F2* were 57.1% (CC), 34.1% (CT), and 7.7% (TT). No significant deviations from the Hardy–Weinberg equilibrium were observed. The frequency of the polymorphisms in the Russian population was found to differ from Asian and close to Caucasian. There were no significant interethnic variations in the frequency of *CYP4F2* among Russian, Asian, and Caucasian populations.

Conclusion. The frequency of *CYP2C9*, *CYP4F2*, and *VKORC1* polymorphisms in Russian patients is comparable with other European ethnic groups.

Introduction

Warfarin is widely used for the prevention and the treatment of venous thromboembolism (VTE) but has a narrow therapeutic index. The most frequent indications for this drug are atrial fibrillation, deep venous thrombosis of the limbs, and stroke (1–3). VTE is unprovoked in 46.0% of patients (4). Patients with atrial fibrillation are at a substantial risk of stroke, which is modified by the presence or the absence of several risk factors (5). The current estimate of the prevalence of atrial fibrillation in the developed world is approximately 1.5%–2% of the general population, with a mean age of patients with this condition steadily rising (6). Warfarin is recommended for patients with atrial fibrillation with risk factors (Class I recommendations) (6).

Bleeding, the major complication of oral anticoagulant therapy, is closely related to the intensity of anticoagulation, use of several drugs affecting platelet adhesion, or production of vitamin K-dependent proteins. Other factors associated with a higher risk of bleeding include a history of stroke and the presence of a serious comorbid condition, such as renal insufficiency, anemia, or hypertension. The contra-

indications for warfarin are coagulopathies, active gastrointestinal bleeding, hemorrhagic retinopathy, uncontrolled hypertension, and pregnancy (7–10).

Oral anticoagulant therapy requires a permanent control of the international normalized ratio (INR). The earliest changes in the INR showing an anticoagulant activity are typically observed 24–36 hours after drug administration (due to the clearance of factor VII), but antithrombotic activity is not present until the fifth day of the therapy, which is due to the clearance of factor II (11). High-quality dose management is needed to achieve and maintain the INR in the therapeutic range. The recommendation of a target INR of 2.0 to 3.0 is supported by the following evidence: an indirect comparison of several randomized trials has shown that a moderate-intensity warfarin regimen (INR, 2.0 to 3.0) resulted in a similar risk reduction as higher-intensity regimens (10). Warfarin users with no in-facility INR monitoring have the greatest risk of stroke; however, hemorrhagic complications may be minimized with frequent monitoring and tight management of a patient's anticoagulation status (11).

Due to some genetic polymorphism, dose adjustment is needed in almost every individual because of variable metabolism of warfarin (12). During the remaining unprotected time periods, especially dur-

Correspondence to D. Ivashchenko, Malaya Pirogovskaya 16, 503-3, 119435 Moscow, Russia. E-mail: dvi1991@yandex.ru

ing the initiation of therapy, patients may be at an increased risk of hemorrhagic or thromboembolic complications (13, 14). A new approach is individualized warfarin dosing according to the results of a pharmacogenetic test (15). Modeling the requirements of a stable dose taking into account clinical, physiological, environmental, and genetic factors has shown promise as a strategic approach to predict individually tailored stable warfarin dose requirements (15, 16).

There are 2 polymorphisms of cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) genes that affect a warfarin dose. Patients who are poor metabolizers of warfarin (alleles *CYP2C9**2 and *3) require reduced maintenance doses compared with those having wild-type alleles (15–19).

Warfarin affects coagulation through the inhibition of *VKORC1* in hepatocytes. *VKORC1* converts vitamin K epoxide to vitamin K hydroquinone, which is an essential cofactor for the carboxylation of clotting factors II, VII, IX, and X. The polymorphism –1639 G/A of the *VKORC1* promoter sequence causes a decreased activity of the enzyme. Patients with this polymorphism require a lower warfarin maintenance dose. The presence of *CYP2C9* and *VKORC1* polymorphisms may explain up to 45% of the variability in the warfarin dosing (15, 17, 19).

Recently, the role of the *CYP4F2* enzyme in the metabolism of warfarin has been disclosed. *CYP4F2* is a primary vitamin K1 oxidase in the liver that is involved in the metabolism of vitamin K1 to hydroxylated vitamin K1 and acts as a counterpart of *VKORC1* in limiting an excessive accumulation of vitamin K. The single-nucleotide polymorphisms of *CYP4F2* (rs2108622, V433M) has been found to be associated with warfarin dose variability. Carriers of the *CYP4F2* V433M polymorphism have a reduced capacity to metabolize vitamin K, secondary to an rs2108622-dependent decrease in steady-state hepatic concentrations of the enzyme. Therefore, patients with the rs2108622 polymorphism are likely to have elevated hepatic levels of vitamin K, necessitating a higher warfarin dose to achieve therapeutic anticoagulation (20).

The prevalence of the *CYP4F2* polymorphisms has been studied relatively recently. Studies confirm that the *CYP4F2* rs2108622 gene really affects an average warfarin dose (16, 21).

There are no studies about the prevalence of the *CYP4F2* polymorphism in Russian patients who are prescribed warfarin. The aim of the present study is to investigate the genetic variability of *CYP2C9* (*1, *2, *3), *VKORC1* –1639 G/A and *CYP4F2* V433M rs2108622 genes with the help of real-time polymerase chain reaction in the Russian patients who required warfarin in the outpatient setting.

Material and Methods

A total of 91 Caucasian subjects from Moscow and Moscow region participated in the study. All the patients had indications to receive warfarin (atrial fibrillation, deep venous thrombosis, mechanical heart valve replacement, etc.). The medical records of the patients were reviewed for the relevant clinical data. Genotype information charts were used in the study. All the patients had a high risk of thrombosis (CHA2DS2-VASc score of >1). Some of the patients received amiodarone and statins. The characteristics of the patients are presented in Table 1.

The INR was calculated for each patient. Warfarin dosing was carried out based on *CYP2C9*, *VKORC1*, and *CYP4F2* genotyping using the algorithm (22). The calculated mean dose of warfarin was 4.22±1.99 mg per day.

Blood (5 mL) was taken from each subject. DNA was isolated and used for the identification of *CYP2C9* (*1, *2, *3), –1639G/A *VKORC1*, and *CYP4F2* V433M rs2108622 C>T using the real-time polymerase chain reaction-restriction fragment length polymorphism assay. The chi-square test and correlation analysis were applied. A *P* value of <0.05 was considered as statistically significant.

Results

The *CYP2C9**1/*1 genotype was detected in 61 (67.0%) patients, *CYP2C9**1/*2 in 9.9%, *CYP2C9**1/*3 in 11.0%, *CYP2C9**2/*2 in 2.2%,

Table 1. Characteristics of the Study Population

Characteristic	Value
Clinical data	
Age, years	66.17 (11.89)
Weight, kg	82.4 (16.4)
Height, cm	169 (9.6)
Male, n (%)	42 (46)
Female, n (%)	49 (53.8)
Smoking, n (%)	10 (11)
Hepatitis, n (%)	2 (2.2)
Indication to receive warfarin, n (%)	
Atrial fibrillation	59 (64.8)
Deep venous thrombosis	19 (20.9)
Mechanical heart valve replacement	3 (3.3)
Other indications	15 (16.5)
Dosage initial parameters, mg	
Dose of warfarin	4.22 (1.99)
Initial INR	1.05 (0.12)
Targeted INR	2.38 (0.28)
Concomitant therapy, n (%)	
Amiodarone 100 mg	3 (3.3)
Amiodarone 200 mg	7 (7.7)
Amiodarone 400 mg	2 (2.2)
Amiodarone 600 mg	1 (1.1)
Statins 10 mg	11 (9.9)
Statins 20 mg	2 (2.2)

Values are mean (standard deviation) unless otherwise stated. INR, international normalized ratio.

*CYP2C9**2/*3 in 8.8%, and *CYP2C9**3/*3 in 1.1% of the patients. The prevalence of *VKORC1* was 49.5% (GG), 28.6% (GA), and 22.0% (AA), and that of the *CYP4F2* genotype was 57.1% (CC), 34.1% (CT), and 7.7% (TT). The *CYP2C9**1 allele was documented in 77% of the patients, *CYP2C9**2 in 12%, and *CYP2C9**3 in 11%; the *VKORC1* allele G was found in 64% and allele A in 36% of the cases; 74% of the patients were carriers of the *CYP4F2* allele C and 25% of allele T. No significant deviations from the Hardy-Weinberg equilibrium were observed (Table 2). The frequency of the polymorphisms in the Russian population differs from Asian and is close to Caucasian (Tables 3 and 4). There were no significant interethnic variations in the prevalence of *CYP4F2* among Russian, Asian, and Caucasian populations (Table 5).

The correlation analysis showed no significant associations between the genotypes and other characteristics of the patients.

Discussion

The prevalence of the *CYP2C9* and *VKORC1* genotypes in different populations, as well as their influence on the achievement of a therapeutic dose of warfarin, has been actively studied. The carriage of allelic variants depends on the ethnic group of pa-

tients (15, 23, 26). Laboratory tests for the *CYP2C9* and *VKORC1* polymorphisms are commercially available, but their use during warfarin treatment has been very limited. Without data substantiating the clinical utility of warfarin genotyping, many clinicians have been reluctant to apply warfarin sensitivity testing in standard practice (19).

There are some studies regarding the carriage of the *CYP2C9* and *VKORC1* polymorphisms in Russian patients. Sirotkina et al. in 2005 investigated the allele variants of cytochrome *CYP2C9* in patients in Saint Petersburg and reported that 82.66% of the patients had *CYP2C9**1, 11.11% had *CYP2C9**2, and 6.32% had *CYP2C9**3. The carriers of the *CYP2C9**2 and *CYP2C9**3 alleles more rapidly achieved the target INR and required significantly lower weekly doses of warfarin (15). However, the authors reported the results only for the *CYP2C9* alleles and not for genotypes. Vorob'eva et al. in 2011 studied the polymorphisms of the *CYP2C9* and *VKORC1* genes in patients with thromboembolic complications in Moscow popula-

Table 2. Prevalence of *CYP2C9*, *VKORC1*, and *CYP4F2* and Chi-Square Test Results for the Hardy-Weinberg Equilibrium

Polymorphism	Prevalence, %	P
<i>CYP2C9</i>		
*1/*1	67.0	0.913
*1/*2	9.9	
*1/*3	11.0	
*2/*2	2.2	
*2/*3	8.8	
*3/*3	1.1	
<i>VKORC1</i>		
GG	49.5	0.972
GA	28.6	
AA	22.0	
<i>CYP4F2</i>		
CC	57.1	0.869
CT	34.1	
TT	7.7	

Table 3. Prevalence of *CYP2C9* in Different Populations

Population	<i>CYP2C9</i>						Reference
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	
Russian	67.0*	9.9*	11.0*	2.2	8.8	1.1	Present study (23) (24) (18) (23)
Chinese	96.5*	0.1*	3.4*	NA	NA	NA	
Caucasian	53.3*	16.8*	21.9*	1.1	4.7	NA	
Russian	84.7*	4.5*	10.8*	NA	NA	NA	
Japanese	97.8*	0.0*	2.2*	NA	NA	NA	

Values are percentage. NA, not available.

* $\chi^2=18.73$, $P<0.001$; comparing the prevalence of *CYP2C9**1/*1, *1/*2, and *1/*3 between Russian/Caucasian and Asian patients. $\chi^2=0.625$, $P=0.42$; comparing of the prevalence of *CYP2C9**1/*1, *1/*2, and *1/*3 between Russian and Caucasian patients.

Table 4. Prevalence of *VKORC1* in Different Populations

Popula- tion	<i>VKORC1</i>			Reference
	GG	GA	AA	
Russian	49.5	28.6	22.0	Present study (25) (18)
Asian	2.1	34.3	63.6	
Russian	42.3	48.6	9.1	
	$\chi^2=34.947$, $P<0.0001$	$\chi^2=0.74$, $P=0.39$	$\chi^2=4.96$, $P=0.02$	

Values are percentage.

Table 5. Prevalence of *CYP4F2* in Different Populations

Population	<i>CYP4F2</i>			Reference
	TT	CT	CC	
Russian	7.7	34.1	57.1	Present study (27) (21)
Asian	7	41	52	
Caucasian	8.4	37.1	54.4	

Values are percentage.

$\chi^2=0.695$, $P=0.404$; comparing the prevalence of *CYP4F2* TT, CT, and CC between Russian and Asian patients.

$\chi^2=0.034$, $P=0.85$; comparing the prevalence of *CYP4F2* TT, CT, and CC between Russian and Caucasian patients.

tion. The *CYP2C9**1/*1 genotype was detected in 84.7% of patients. Other genotypes were also detected: *CYP2C9**1/*2 in 4.5% and *CYP2C9**1/*3 in 10.8% of the patients. *VKORC1* genotyping demonstrated that 42.3% of the patients carried the *GG* genotype; 48.6%, the *GA* genotype; and 9.1%, the *AA* genotype. The carriers of the *CYP2C9**1/*3 and *VKORC1* polymorphisms showed less stable anticoagulation in comparison with the carriers of *CYP2C9**1/*1, *CYP2C9**1/*2, and the *VKORC1* *GG* and *GA* genotypes (14). Pchelina et al. enrolled in their study 298 persons from Saint Petersburg, and 62 of them received warfarin. The authors investigated the prevalence of the *CYP2C9* polymorphisms and determined the time needed to achieve therapeutic anticoagulation for different allelic variants (18). Sirotkina et al. and Pchelina et al. analyzed only *CYP2C9* and did not take into account *VKORC1* (15, 18). The findings of the Russian studies are shown in Tables 3 and 6.

The influence of the *CYP4F2* polymorphisms on warfarin metabolism has been already proven (16, 19, 27). Therefore, this genotype must be investigated together with *CYP2C9* and *VKORC1* in order to analyze haplotypes. A study on the role of

CYP4F2 in the achievement of a therapeutic warfarin dose has been conducted among Russian patients (28). The authors investigated the influence of the *CYP2C9*, *VKORC1*, and *CYP4F2* polymorphisms on a warfarin dosage. This study reported that the presence of the *VKORC1* and *CYP2C9**3 polymorphisms explained 19.58% of the variability in a warfarin dose. This study did not detect any impact of *CYP4F2* on the dose of warfarin.

Our data are different from the results of similar studies in other ethnic groups (23–27, 29). Major differences were observed between the Caucasian and Asian populations. For example, no *CYP2C9**1/*2 genotype was determined in Asians, but *CYP2C9**1/*1 was determined in 96% of the cases (53% in Caucasians [27] and 68% in Russians [14]). *VKORC1* *GG* is the rarest genotype among Asians, and *VKORC1* *AA* is the most common. There are no significant differences among Russian patients (14, 18, 23). The prevalence of the *CYP4F2* polymorphisms is not significantly different between Russian, Caucasian, and Asian populations (19, 25). However, all the studies on this genotype have been carried out relatively recently, and further research into its prevalence and influence on a warfarin dosage is needed.

Table 6. Prevalence of *CYP2C9* in the Present Study and Other Russian Studies

	<i>CYP2C9</i>						Reference
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	
Patients	67.0	9.9	11.0	2.2	8.8	1.1	Present study
Population	84.7	4.5	10.8	NA	NA	NA	(18)
Population	67.9	18.1	11.1	1.3	1.3	0.3	(14)
Patients	73.0	15.9	7.9	1.6	NA	NA	(14)

Values are percentage. NA, not available.

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Conclusions

We defined the prevalence of *CYP2C9*, *VKORC1*, and *CYP4F2* in the Russian patients with a high thrombotic risk. Further prospective research is necessary with a new algorithm of warfarin dosing taking into account all the genotypes. The results of the present study will be used for further investigations into warfarin dosing depending on the genotype.

Statement of Conflict of Interest

The authors state no conflict of interest.

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