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

Dmitriy Ivashchenko[1], Ilya Rusin[1], Dmitriy Sychev[2], Andrey Grachev[3]
[1]I. M. Sechenov First Moscow State Medical University,
[2]Russian Medical Academy of Postgraduate Education, [3]SM-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 contraindications 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 *VCORC1*, 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 patients (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*
CYP2C9		
**1/*1*	67.0	
**1/*2*	9.9	
**1/*3*	11.0	0.913
**2/*2*	2.2	
**2/*3*	8.8	
**3/*3*	1.1	
VKORC1		
GG	49.5	0.972
GA	28.6	
AA	22.0	
CYP4F2		
CC	57.1	
CT	34.1	0.869
TT	7.7	

Table 4. Prevalence of *VKORC1* in Different Populations

Population	*VKORC1*			Reference
	GG	*GA*	*AA*	
Russian	49.5	28.6	22.0	Present study
Asian	2.1	34.3	63.6	(25)
Russian	42.3	48.6	9.1	(18)
	χ^2=34.947, *P*<0.0001	χ^2=0.74, *P*=0.39	χ^2=4.96, *P*=0.02	

Values are percentage.

Table 5. Prevalence of *CYP4F2* in Different Populations

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

Values are percentage.
χ^2=0.695, *P*=0.404; comparing the prevalence of *CYP4F2* TT, CT, and CC between Russian and Asian patients.
χ^2=0.034, *P*=0.85; comparing the prevalence of *CYP4F2* TT, CT, and CC between Russian and Caucasian patients.

Table 3. Prevalence of *CYP2C9* in Different Populations

Population	*CYP2C9*						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
Chinese	96.5*	0.1*	3.4*	NA	NA	NA	(23)
Caucasian	53.3*	16.8*	21.9*	1.1	4.7	NA	(24)
Russian	84.7*	4.5*	10.8*	NA	NA	NA	(18)
Japanese	97.8*	0.0*	2.2*	NA	NA	NA	(23)

Values are percentage. NA, not available.
*χ^2=18.73, *P*<0.001; comparing the prevalence of *CYP2C9*1/*1, *1/*2*, and **1/*3* between Russian/Caucasian and Asian patients.
χ^2=0.625, *P*=0.42; comparing of the prevalence of *CYP2C9*1/*1, *1/*2*, and **1/*3* 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

	CYP2C9						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.

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.

References

1. Schelleman H, Chen J, Chen Z, Christie J, Newcomb CW, Brensinger CM, et al. Dosing algorithms to predict warfarin maintenance dose in Caucasians and African Americans. Clin Pharmacol Ther 2008;84:332-9.
2. Palacio L, Falla D, Tobon I, Mejia F, Lewis JE, Martinez AF, et al. Pharmacogenetic impact of VKORC1 and CYP2C9 allelic variants on warfarin dose requirements in a hispanic population isolate. Clin Appl Thromb Hemost 2010;16:83-90.
3. Kassab MM, Radmer TW, Glore JW, Visotcky A, Robertson J, Degroot B. A retrospective review of clinical international normalized ratio results and their implications. J Am Dent Assoc 2011;142:1252-7.
4. Kahn SR, Springmann V, Schulman S, Martineau J, Stewart JA, Komari N, et al. Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. The Recovery Study. Thromb Haemost 2012;108:493-8.
5. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study BMJ 2011;342:d124.
6. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation.
7. Ansell J, Hirsh J, Dalen J, Bussey H, Anderson D, Poller L, et al. Managing oral anticoagulant therapy. Chest 2001;11:22S-38S.
8. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160-98.
9. Hull R, Hirsh J, Jay R, Carter C, England C, Gent M, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982;307:1676-81.
10. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. Cleve Clin J Med 2003;70:361-71.

11. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, et al.; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29(18):2276-315.
12. Moyer TP, O'Kane DJ, Baudhuin LM, Wiley CL, Fortini A, Fisher PK, et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. Mayo Clin Proc 2009;84:1079-94
13. Limdi NA, McGwin G, Goldstein JA, Beasley TM, Arnett DK, Adler BK, et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. Clin Pharmacol Ther 2008;83:312-21.
14. Vorob'eva NM, Panchenko EP, Dobrovol'skiĭ AB, Titaeva EV, Khasanova ZB, Konovalova NV, et al. Polymorphisms of genes CYP2C9 and VKORC1 in patients with venous thromboembolic complications in Moscow population: effects on stability of anticoagulant therapy and frequency of hemorrhage. Ter Arkh 2011;83:59-65.
15. Sirotkina OV, Ulitina AS, Taraskina AE, Kadinskaia MI, Vavilova TV, Pchelina SN, et al. Clinical value of allele variants of cytochrome CYP2C9 gene for anticoagulation therapy with warfarin. Kardiologiia 2005;45:61-3.
16. McDonald MG, Rieder MJ, Nakano M, Hsia CK, Rettie AE. CYP4F2 is a vitamin K1 oxidase: an explanation for altered warfarin dose in carriers of the V433M variant. Mol Pharmacol 2009;75:1337-46.
17. Ruano G, Thompson PD, Villagra D, Bower B, Kocherla M, Yazdanpanah G, et al. High carrier prevalence of combinatorial CYP2C9 and VKORC1 genotypes affecting warfarin dosing. Personalized Medicine 2008;5:225-32.
18. Pchelina SN, Sirotkina OV, Taraskina AE, Vavilova TV, Shwarzman AL, Schwartz EI. The frequency of cytochrome P450 2C9 genetic variants in the Russian population and their associations with individual sensitivity to warfarin therapy. Thromb Res 2005;115:199-203.
19. Danese E, Montagnana M, Johnson JA, Rettie AE, Zambon CF, Lubitz SA, et al. Impact of the CYP4F2 p.V433M polymorphism on coumarin dose requirement: systematic review and meta-analysis. Clin Pharmacol Ther 2012;92:746-56.
20. Sychev DA, Antonov IM, Ignat'ev IV, Naumova IuV, Dmitriev VA, Kropacheva ES, et al. Anticoagulant action and safety of warfarin dosing based on pharmacogenetic testing: results of the first Russian prospective pilot study. Kardiologia 2010;5:42-6.
21. Teichert M, Eijgelsheim M, Rivadeneira F, Uitterlinden AG, van Schaik RH, Hofman A, et al. A genome-wide association study of acenocoumarol maintenance dosage. Hum Mol Genet 2009;18:3758-68.
22. Warfarin dosing. Available from: URL: http://www.warfarindosing.org/Source/Home.aspx
23. Bae JW, Kim HK, Kim JH, Yang SI, Kim MJ, Jang CG, et al. Allele and genotype frequencies of CYP2C9 in a Korean population. Br J Clin Pharmacol 2005;60:418-22.
24. Sipeky C, Lakner L, Szabo M, Takacs I, Tamasi V, Polgar N, et al. Interethnic differences of CYP2C9 alleles in healthy Hungarian and Roma population samples: relationship to worldwide allelic frequencies. Blood Cells Mol Dis 2009; 43:239-42.
25. Kuanprasert S, Dettrairat S, Palacajornsuk P, Kunachiwa W, Phrommintikul A. Prevalence of CYP2C9 and VKORC1 mutation in patients with valvular heart disease in northern Thailand. J Med Assoc Thai 2009;92:1597-601.
26. Caldwell MD, Awad T, Johnson JA, Gage BF, Falkowski M, Gardina P, et al. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111:4106-12.
27. Cen HJ, Zeng WT, Leng XY, Huang M, Chen X, Li JL, et al. CYP4F2 rs2108622: a minor significant genetic factor of warfarin dose in Han Chinese patients with mechanical heart valve replacement. Br J Clin Pharmacol 2010;70:234-40.
28. Belozerceva LA, Voronina EN, Kokh NV, et al. The influence of CYP2C9, VKORC1, CYP4F2, GGCX, PROC, F VII polymorphisms on warfarin dosing in patients from West-Siberia region of Russia. Proceedings of the 1st Russian Conference "Medical and Biological Science: Progress and Perspectives"; 2011; Tomsk, Russia.
29. Epstein RS, Moyer TP, Aubert RE, O'Kane DJ, Xia F, Verbrugge RR, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness Study). J Am Coll Cardiol 2010;55: 2804-12.

Received 12 February 2013, accepted 27 September 2013