The Pharmacogenomics Journal
https://doi.org/10.1038/s41397-020-0157-2

ARTICLE

CYP2C9 and *VKORC1* genotyping for the quality of long-standing warfarin treatment in Russian patients

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Received: 10 May 2019 / Revised: 22 January 2020 / Accepted: 27 January 2020

Abstract

A total of 263 warfarin naive patients with indications to long-term anticoagulation were included in prospective multicenter study and randomized into Pharmacogenetics and Standard dosing groups. The loading warfarin dose in Pharmacogenetics group was calculated by Gage algorithm and corrected starting on day 5 of treatment according to INR. In Standard dosing group warfarin initial dose was 5 mg and starting on day 3 of treatment it was titrated according to INR. Pharmacogenetics dosing in comparison with prescription of starting dose of 5 mg decreased major bleedings (0 vs. 6, $p = 0.031$), time to target INR (11 [9–14] vs. 17 [15–24] days, $p = 0.046$), and frequency of INR fluctuations ≥4.0 (11% vs. 30.9%, $p = 0.002$). The advantages of the pharmacogenetics dosing were mainly achieved due to the patients with increased warfarin sensitivity.

Introduction

Warfarin remains the most commonly prescribed anticoagulant in primary and secondary prevention of thromboembolic disorders associated with atrial fibrillation, mechanical prosthetic valves replacement, and venous thromboembolism [1]. Nevertheless, the initiation of warfarin therapy is complicated by risk of bleedings due to its relatively narrow therapeutic window and high variability of individual maintenance dose, which depends on multiple factors including age, body mass, diet, and concurrently taken medications [2]. Observational studies have shown an association of the individual response to warfarin with common polymorphisms in genes involved in its action and metabolism [3–5].

In Caucasians major genetic determinants of increased warfarin sensitivity are *VKORC1-1639 G > A* (rs9923231) and *CYP2C9 *2* (rs1799853) and **3* (rs1057910) polymorphisms, which along with clinical factors explain about 50% of variability in warfarin dose [5]. Other known genetic factors influencing warfarin sensitivity are *CYP4F2 *3* (rs2108622) and GGCX C > G (rs11676382) [6–8]. However, these polymorphisms influence warfarin sensitivity to a lesser extent than polymorphisms in *VKORC1* and *CYP2C9* and according to CPIC Guideline (2017 update) are considered as optional in pharmacogenetics warfarin dosing [9]. Several algorithms for warfarin dosing have been developed in which genetics data are considered in conjunction to clinical and demographic factors [9–11]. Further studies have shown that the contribution of factors affecting the sensitivity to warfarin may vary markedly between patients from different ethnic groups [9].

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Published online: 06 February 2020

In 2010, the US Food and Drug Administration (FDA) approved the warfarin dosing table based on *CYP2C9* and *VKORC1* genotypes. However, in 2012 guidelines from the American College of Chest Physicians the genotyping for warfarin was not recommended since the conclusions of several randomized trials performed till that time were discrepant, indicating the need for further studies [1].

Current study was performed to compare the standard warfarin dose prescription with dosing based on genotyping for *CYP2C9* and *VKORC1* polymorphisms on the time to reach the target INR, stability of anticoagulation, and bleeding complications during first 6 months of treatment.

Methods

Protocol

Warfarin naive patients of age 18 or older, who were planned to receive anticoagulant treatment for at least 6 months, were included in the study. Inclusion criteria were any indication for long-term VKA treatment (non-valvular atrial fibrillation with CHA_2DS_2Vasc ≥2 in men and ≥3 in women, venous thromboembolism, mechanical prosthetic valves and thrombus in left ventricle). Exclusion criteria were refusal to participate, active cancer, pregnancy, concomitant use of nonsteroidal anti-inflammatory drugs, and other anticoagulants.

Outpatients and inpatients were recruited at eight centers from Northwest, Central, Ural, and Siberian regions of Russia. All patients have signed the written informed consent. The study complies with the Helsinki Declaration, EU Directives. The protocol of the study was approved by Russian Cardiology Society and National Society of Atherothrombosis.

The study was randomized and open-label. Patients have been randomized by envelop method in a 1:1 ratio into either Pharmacogenetics or Standard dosing groups. In Pharmacogenetics group the loading and therapeutic doses of warfarin have been calculated by Gage algorithm [10]. Gage algorithm was chosen because it is in free access in the internet and therefore is most popular in Russia.

This dosing algorithm does take into account the revealed *CYP2C9* and *VKORC1* polymorphisms in a tight consideration with other clinical and demographic characteristics of the patient. After getting results of INR on day 5 of treatment, the warfarin dose was corrected upon necessity. In Standard group warfarin was prescribed at initial dose of 5 mg/day. The therapeutic warfarin dose was titrated, starting at the third day of treatment.

In both groups medical examination and INR control were performed at baseline, on day 3, then every 2–3 days during the first 2 weeks of treatment, by the end of weeks 3 and 4, and thereafter monthly. Warfarin dose was titrated until the therapeutic range (TTR) (INR between 2.0 and 3.0) has been achieved and maintained, at least, for two consecutive visits. In case of any complications additional visits for INR control have been allowed.

For all patients blood samples were collected for genotyping at first visit and shipped to the central laboratory by express-mail. Genotyping for *CYP2C9* and *VKORC1* was reported to local centers within 24 h after blood collection for Pharmacogenetics group. In Standard dosing group *CYP2C9* and *VKORC1* polymorphisms have been analyzed upon completion of the follow-up period.

Outcome measures

The primary outcome was the time (days) to reach a stable warfarin dose, which was defined as the time to the first of two consecutive INR values, which were in the TTR without a dose change. Secondary outcomes included the time in the TTR, frequency of INR fluctuations >4.0 and bleedings during the first month and six months of follow up. We also analyzed predictors of more than 20% difference between maintenance and calculated by Gage algorithm doses.

Bleeding complications. Major bleeding was defined according to the Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT) definitions [12]. They included fatal hemorrhage, intracranial bleeding documented by imaging or autopsy, or symptomatic bleeding requiring overnight hospitalization or major therapeutic intervention (transfusion, angiographic intervention, or surgery). All other bleeding episodes were classified as minor.

Genotypes were determined for *CYP2C9 (*2* and **3* alleles*)* and *VKORC1 (-1639 G→A)*. Genotyping was done at DNA-Technology Ltd, Russian Federation.

INR measurement. All centers used an automated coagulometers and thromboplastins from the same manufacturer: STA/Neoplastin, Sysmex CA-500/Tromborel S, ACL-7000/PT fibrinogen HS plus. In order to evaluate the consistency of the INR measurement done by local laboratories with different instrument/reagent combinations all participants were asked to determine in duplicate the INR for two control samples. The deviation of the INR calculated as percentage of ratio: (local value − mean)/mean was ±9.9% for control with mean INR 1.83, and ±13.2% for control with mean INR 2.50. The discrepancy was considered as acceptable.

The time in TTR was calculated as the fraction of INR values within the TTR divided by the total number of INR measured during analyzed period.

Statistical analysis

The sample size was estimated based on the data concerning TTR in Russian patients from the RE-LY trial. According to this data, the mean TTR in Russia was 53%. To identify a difference of 10% between groups in percentage of TTR out of range with a 90% power and an α of 0.05 and assuming a standard deviation of 23% and a drop-out rate of 15%, 133 patients per group are needed to be enrolled.

The Statistical analyses were performed with the Statistical Analysis System package of nonparametric statistics methods. Categorical data are reported as frequencies (percentage), whereas continuous variables are expressed as median and IQR. Statistical significance was set at $p < 0.05$. Group differences were analyzed using nonparametric tests: Mann–Whitney *U* test and two-tailed exact Fisher's test. Stepwise discriminant functional analysis was used to determine the prognostic value of variables influencing the accuracy of Pharmacogenetics warfarin dosing.

Results

Overall, 283 naive patients have been enrolled in the study. Twenty participants (eleven from Pharmacogenetics group and nine from Standard dosing group) have been withdrawn from the study because of discrepancy with inclusion criteria ($n = 5$), allergic reaction to warfarin ($n = 1$), and failure of adherence to required INR control ($n = 14$). At last, data of 263 patients were subjected to final statistical analysis.

There were no significant between-group differences at baseline characteristics of the patients: the primary indications for warfarin and comorbid conditions (Table 1). In both groups, patients were balanced with respect to concomitant medications such as CYP2C9 inhibitors and antiplatelet drugs that could be potential confounding variables. Groups were also well matched for HAS-BLED score, previous bleeding, stroke, and myocardial infarction. The geographic distribution was also balanced. Participants in each group were drawn from Northwest, Central, Ural, and Siberian regions of Russia.

Genetic variables

The genotype distribution of enrolled patients is shown in Table 2. Most of the patients (68.82%) were carriers of wild-type cytochrome CYP2C9*1/*1. The most frequent allelic variants of *CYP2C9* were 1*2 (13.31%) and 1*3 (12.92%). The total frequency of homozygous or compound heterozygous variants *2/*2, *2/*3, and *3/*3 was 4.94%. The *GG, GA*, and *AA* genotypes of *VKORC1* were identified in 39.92%, 44.1%, and 15.97% of patients, respectively. The frequencies of *CYP2C9**2, *CYP2C9**3, and *VKORC1G/A* polymorphisms were similar to the previously reported in Europeans [13].

Outcomes

The impact of genotyping on main outcomes is summarized in Table 3. Clearly, the interval needed to target INR achievement was significantly shorter in Pharmacogenetics group than in Standard dosing group: 11 [9–14] vs. 17 [15–24] days, respectively ($p = 0.046$). In addition, the percentage of patients with INR fluctuations ≥4.0 from 7th till 30th day was also significantly lower in Pharmacogenetics than in Standard dosing group: 11% vs. 30.9% ($p = 0.002$).

However, these differences did not translate into significant improvement of TTR either for the period from day 7 till day 30 after the initiation of warfarin therapy (71 [50–80] vs. 50 [33–67]), or over the entire 6 months (75 [60–86] vs. 75 [50–83]) of follow up. Nevertheless, the percentage of patients with TTR ≥ 70% from the day 7 till day 30 of treatment was two times higher in Pharmacogenetics group than in Standard dosing group: 49.6% vs. 23.5% ($p = 0.0000$).

In both groups the majority of bleeding events occurred during the first month of therapy (Table 3). There was no significant difference in the frequency of overall bleeding between groups. However, all six major bleedings were registered in Standard dosing group. It is worthwhile to mention that five out of six major bleeding incidences developed in carriers of at least one of polymorphisms increasing warfarin sensitivity and were associated with excessive INR (≥3.4).

We analyzed separately bleedings which could be attributed to warfarin overdosing (INR fluctuations ≥4.0). The frequency of these bleedings was significantly lower in Pharmacogenetics than in Standard dosing group. This difference became apparent by the end of the first month of treatment (3.2% vs. 11.0%; $p = 0.038$) and persisted during 6 months of follow up (4.7% vs. 13.2%; $p = 0.038$). During the follow-up period there were no significant differences between groups in bleedings occurring within TTR of INR.

We additionally grouped patients by combinations of *CYP2C9* and *VKORC1* genotypes in genotype functional bins that corresponded to the FDA categories for response in the updated warfarin label: normal, sensitive, and highly sensitive respondents. Due to the small number of highly sensitive patients, we found it possible to combine sensitive and highly sensitive patients into one group. Normal respondents—carriers of *VKORC1 GG/GA* or *CYP2C9*1/*1; *1/*2* genotypes included 183 patients (69.6%). Sensitive respondents—carriers of *CYP2C9*1/*3* or two or more polymorphisms in *VKORC1* or *CYP2C9* genes

Table 1 Baseline characteristics of the study patients.

Characteristic	Pharmacogenetics group ($n = 127$)	Standard dosing group ($n = 136$)	p value
Median age [IQR] year	61 [53–70]	64 [57–71]	0.827
Men, (%)	46.5	56.6	0.426
Indications for VKA			
Nonvalvular atrial fibrillation, (%)	65.4	68.4	1.000
Venous thromboembolism, (%)	22.0	23.5	0.912
Mechanical prosthetic valves, (%)	9.4	7.4	0.657
Other, (%)	3.1	0.7	0.225
CHA_2DS_2-VASc Score for patients with NVAF, median [IQR]	3 [3–5]	3 [2–4]	0.447
Number of NVAF patients with CHA_2DS_2-VASc ≥2, (%)	92.9	92.6	1.000
Previous stroke/TIA/SE, (%)	21.3	16.2	0.436
CAD, (%)	37.8	34.6	0.723
Prior MI, (%)	19.7	15.4	0.532
Stable angina, (%)	31,5	30,1	0.901
Diabetes mellitus, (%)	16.5	11.8	0.447
Hypertension, (%)	77.2	85.3	0.643
Heart Failure, (%)	21.3	18.4	0.645
Chronic kidney disease, (%)	4.7	8.8	0.235
HAS-BLED score, median [IQR]	2 [1–2]	2 [1–2]	1.000
Prior major bleeding, (%)	7.1	5.1	0.621
Prior minor bleeding, (%)	15.8	16.9	0.917
Concomitant aspirin or/and clopidogrel treatment, (%)	15.7	14.7	0.913
Warfarin monotherapy, (%)	84.3	85.6	1.000
Amiodarone, (%)	11	16.9	0.346
Statins, (%)	44.9	44.8	1.000
Genetic variants			
Patients with **1/*1 CYP2C9* and *GG VKORC$_1$* genotype, (%)	26.8	28.6	0.916
Carriers of single polymorphism in *CYP2C9* or *VKORC$_1$* genes, (%)	36.2	44.9	0.346
Carriers of ≥2 variant alleles (*2/*2, *3/*3,*2/*3 *CYP2C9* or *AA VKORC$_1$* or combination of heterozygous variants of both *CYP2C9* and *VKORC$_1$*), (%)	37.0	26.5	0.242

Group differences were analyzed using nonparametric tests: Mann–Whitney *U* test and two-tailed exact Fisher's test.

NVAF nonvalvular atrial fibrillation, *TIA* transient ischemic attack, *SE* systemic embolism, *CAD* coronary artery disease, *MI* myocardial infarction.

included 80 patients (30.4%). Median TTR during the period of therapy was similar in normal and sensitive respondents—75 [60–86] and 75 [50–83], respectively. The median maintenance daily dose of warfarin decreased with increasing total number of *VKORC1* and *CYP2C9* variant alleles and in normal and sensitive respondents respectively amounted to 6.25 [5.0–8.1] and 3.4 [2.5–4.4] mg, $p = 0.035$. The frequency of any bleedings during first month therapy which could be attributed to warfarin overdosing (INR fluctuations ≥ 4.0) was lower in normal than in sensitive respondents, respectively, 4.37% and 13.75%, $p = 0.017$.

We compared main outcomes in sensitive respondents distributed to Pharmacogenetics ($n = 42$) or Standard ($n = 38$) dosing groups (Table 4). The target INR in 14 days after initiation of therapy was achieved in 29 (69.0%) patients of Pharmacogenetics group and only in nine (23.7%) patients of Standard dosing group, $p = 0.0001$. The frequency of INR fluctuations ≥4.0 and any bleedings associated with INR ≥ 4.0 during the first month of therapy were also

Table 2 Genotypes distribution in the study patients.

VKORC1	*CYP2C9* (%)						
	*1/*1 *n* (%)	*1/*2 *n* (%)	*1/*3 *n* (%)	*2/*2 *n* (%)	*2/*3 *n* (%)	*3/*3 *n* (%)	Total *VKORC1* *n* (%)
G/G *n* (%)	73 (27.75)	22 (8.37)	7 (2.66)	1 (0.38)	2 (0.76)	0	105 (39.92)
A/G *n* (%)	78 (29.66)	10 (3.80)	20 (7.60)	3 (1.14)	5 (1.90)	0	116 (44.10)
A/A *n* (%)	30 (11.41)	3 (1.14)	7 (2.66)	0	1 (0.38)	1 (0.38)	42 (15.97)
Total *CYP2C9* *n* (%)	181 (68.82)	35 (13.31)	34 (12.92)	4 (1.52)	8 (3.04)	1 (0.38)	263 (99.99)

Table 3 Main outcomes in study patients.

Characteristic	Pharmacogenetics group, $n = 127$	Standard dosing group, $n = 136$	p value
Interval to target INR achievement, days Median [IQR]	11 [9–14]	17 [15–24]	0.046
Frequency of INR fluctuations > 4.0 from day 7 to day 30[a], (%)	11.0	30.9	0.002
Time in therapeutic range (TTR) from day 7 to day 30[a], (%) Median [IQR]	71 [50–80]	50 [33–67]	0.092
Time in therapeutic range (TTR) over 6 months, Median [IQR]	75 [60–86]	75 [50–83]	0.459
Patients with TTR ≥ 70% from day 7 to day 30[a], (%)	49.6	23.5	0.0000
Total bleedings during 1st month, (%)	12.6	15.4	0.601
Total bleedings during 6 months follow up, %	17.3	22.1	0.451
Major	0	4.4	0.031
Minor	17.3	17.7	1.000
Total bleedings during 1st month in patients with INR > 4.0, (%)	3.2	11.0	0.038
Total bleedings with INR > 4.0 during 6 months, (%)	4.7	13.2	0.038

Group differences were analyzed using nonparametric tests: Mann–Whitney *U* test and two-tailed exact Fisher's test.

[a] It was calculated as the fraction of all INR values within the therapeutic range from day 7 to day 30 of warfarin treatment.

Table 4 Main outcomes in sensitive warfarin respondents.

	Sensitive respondents—carriers of *CYP2C9*1/*3* or two or more polymorphisms in *VKORC1* or *CYP2C9* genes, $n = 80$		
	Pharmacogenetics group, $n = 42$	Standard dosing group, $n = 38$	p value
Achievement of target INR by day 14, *n* (%)	29 (69)	9 (23.7)	0.0001
Frequency of INR ≥ 4.0 from day 7 to day 30[a], *n* (%)	10 (23.8)	20 (52.6)	0.011
Total bleedings during first month in patients with INR ≥ 4.0, *n* (%)	2 (4.76)	9 (23.7)	0.021

[a] It was calculated as the fraction of all INR values from day 7 to day 30 of treatment.

significantly lower in Pharmacogenetics group than in Standard dosing group: 23.8% vs. 52.6% ($p = 0.011$) and 4.8% vs. 23.7% ($p = 0.021$), respectively.

Accuracy of pharmacogenetics dosing

We retrospectively calculated the predicted warfarin dose also for patients of Standard dosing group by Gage algorithm and combined data of both groups to identify variables that could have an impact on the accuracy of Pharmacogenetics dosing in Russian patients. The predicted dose coincided within ±20% of the actual therapeutic dose in 150 patients (57%), was less than calculated in 89 patients (33.8%), and was higher than calculated in 24 patients (9.1%).

To establish the factors associated with the difference of more than 20% between predicted by Gage algorithm and actual warfarin doses we applied discriminant function analysis. All demographic, clinical, and genetic variables with potential impact on warfarin dose were included into analysis. Two variables: "intake of any of amiodarone dose within 30 days" and "*VKORC1AA* genotype" were associated with overestimation of calculated warfarin dose (Table 5). Another two variables: "absence of heart failure" and "alcohol consumption" were associated with underestimation of calculated warfarin dose (Table 5).

Table 5 Variables influencing the accuracy of warfarin dosing by Gage algorithm in Russian population (discriminant function analysis).

Variables	F-remove	*p* value
Overestimation of calculated dose		
Any amiodarone intake within 30 days	7.78	0.005
Genotype *VCORC1 AA*	3.8	0.043
Underestimation of calculated dose		
Absence of heart failure	5.24	0.023
Alcohol consumption	3.98	0.047

Discussion

Vitamin K antagonists, such as warfarin, are commonly used anticoagulants to prevent and treat thromboembolic disease. However, the use of warfarin is hampered by several reasons including variable patient's response to the drug, the necessity to monitor and adjust warfarin dose for each patient, as well as bleedings, associated with the use of warfarin. Bleedings are the most important complications related to narrow therapeutic window and high variability of individual warfarin dose.

Clear association of interindividual variability in the response to warfarin with common polymorphisms in genes involved in its action and metabolism was shown more than 15 years ago [3, 4]. Nevertheless, the advisability of genotyping before prescription of warfarin is still under discussion [9, 11]. The main obstacle, limiting the implementation of Pharmacogenetics dosing to clinical practice, was the absence of definite evidence that genotyping increases efficacy or safety of the therapy. However, to obtain such evidence it is necessary to perform large-scale trials. Even in the two currently largest randomized trials, which enrolled 1597 and 2264 patients, only a tendency toward a lower risk of clinically relevant bleeding or thromboembolism was observed [14, 15]. Therefore in the majority of trials primarily the laboratory predictors of negative outcomes such as TTR, INR fluctuation > 4, or time to target INR were evaluated.

During the last 15 years, the utility of Pharmacogenetics dosing was analyzed in numerous studies, including more than 20 prospective randomized trials [14–33]. Although these studies arrived at inconsistent conclusions, results of three recent meta-analyses, which pooled data from trials published by end of 2017, indicate that Pharmacogenetics dosing improved laboratory indexes of anticoagulation control and reduced the risk of major bleeding when compared with conventional dosing (either standard starting dose or clinically guided dosing) [34–36]. Subgroup analysis demonstrated the superiority of Pharmacogenetics dosing over prescription of standard starting dose. But in the studies, where the initial dose of warfarin in the control group was determined by taking into consideration clinical factors, the advantage of Pharmacogenetics dosing was less evident [34, 35]. This conclusion could be expected. The polymorphisms of *CYP2C9* and *VKORC$_1$* genes may exert great influence on the patient sensitivity to warfarin. However, this influence is manifested in the carriers of polymorphisms only, whereas the influence of clinical factors is expressed in all patients. Nevertheless, it is the carriers of polymorphisms who have an increased risk of excessive anticoagulation during the initiation of therapy and bleeding, if the starting dose of warfarin is determined without taking into account characteristics of genotype [13, 37].

Our data concerning time to target INR, frequency of INR > 4 during first month of treatment, and major bleeding are in fairly well concordance with conclusions of these meta-analysis.

In our study, the Pharmacogenetics dosing was compared with the most often used in Russia starting warfarin dose of 5 mg, which was titrated from the third day of therapy, depending on the INR value [38]. The choice of 5 mg of warfarin as standard starting dose in the control group, which according to our previous studies corresponds to about 70% of average dose for the population of Russian patients, has been determined by several reasons. Firstly, even in patients with normal metabolism of warfarin the time of its half-elimination is much longer, than the time to warfarin peak concentration in plasma after drug administration [39]. Secondly, INR reacts faster to the increase of warfarin level than to its decrease. This is likely caused by the significant differences in half-life time for factors VII, and II, which are main determinants of the INR [40, 41]. On the basis of these facts it is logically to presume that the time needed to determine the maintenance dose of warfarin would be shorter for cases which require increase but not decrease of starting dose. Also this approach lowers the probability for the development of excessive anticoagulation. Nevertheless it turned out, that the dose of 5 mg was excessive for 40.7% of all included patients and for 77.5% of sensitive respondents.

The close association of *CYP2C9* and *VKORC1* genetic polymorphisms with the risk of over-anticoagulation and bleeding during the initial period of warfarin therapy was revealed in a number of observational studies and recently confirmed by subanalyses of large studies in which warfarin was compared with direct oral anticoagulants [8, 13, 37]. Thus, besides initial warfarin dosing, genotyping for *CYP2C9* and *VKORC1* polymorphisms may be useful to choice optimal oral anticoagulant especially in patients with high bleeding score.

We also analyzed demographic, clinical, and genetic variables which could influence the precision of Gage algorithm in Russian patients. According to discriminant function analysis, two variables: "intake of amiodarone" and "*VKORC$_1$AA* genotype" were associated with

overestimation of calculated warfarin dose. Underestimation of calculated warfarin dose was associated with two variables: "absence of heart failure" and "alcohol consumption".

In our study the frequency of major bleedings in standard dosing group during 6-month follow up was 4.4% that is actually higher than usual for warfarin treated patients. This can be explained by the ISCOAT criteria we used for the major bleeding, which in addition to the traditional definitions includes symptomatic bleeding required overnight hospitalization or major therapeutic intervention [12].

Study limitations

We analyzed only two most common polymorphisms associated with increased warfarin sensitivity. Our study was not powered to detect the difference in thrombotic outcomes. The mean age of patients was about 60 years. There were only 8% of patients with mechanical prosthetic valves and 15% of patients had concomitant aspirin or/and clopidogrel treatment.

Conclusion

Warfarin dosing based on the genotyping for *CYP2C9* and *VKORC1* in comparison with fixed dose of 5 mg significantly decrease major bleeding, time to target INR achievement, and frequency of INR fluctuations ≥ 4.0. The advantages of the Pharmacogenetics dosing were achieved due to the patients with increased warfarin sensitivity, because in those cases the genotype-based dosing ensured not only the faster achievement of target INR, but also decreased the frequency of the INR ≥ 4 fluctuations and related bleedings during the first month of therapy. Extra cost of genotyping may be partially compensated by decreasing the number of clinical visits, INR measurements, and expenses of bleeding treatment.

Acknowledgements The authors appreciate the dedicated help of colleagues and nurses at the hospitals where this study was conducted and thank all participated patients. This study was partially supported by the Fund No. 8/3-280n-10 from the Moscow State Government and by funding from centers participated in this study.

Compliance with ethical standards

Conflict of interest EP reports personal fees and nonfinancial support from Takeda, Pfizer, Boehringer Ingelheim, and Bayer during the conduct of the study; AD reports personal fees and nonfinancial support from Takeda, Instrumentation Laboratory, Diagnostica Stago during the conduct of the study; NV reports personal fees from Bayer, Pfizer, and Takeda, outside the submitted work during the conduct of the study; LG reports personal fees and nonfinancial support from Takeda, personal fees and nonfinancial support from Bayer, personal fees from Pfizer, during the conduct of the study; DZ reports personal fees and nonfinancial support from Takeda, AstraZeneca, Boehringer Ingelheim, and Bayer during the conduct of the study; IZ reports personal fees from Takeda, Pfizer, Boehringer Ingelheim, and Bayer during the conduct of the study; TV reports personal fees and nonfinancial support from Takeda, Pfizer, Boehringer Ingelheim, personal fees and Bayer during the conduct of the study; EK has nothing to disclose; ET has nothing to disclose; OZ has nothing to disclose; DT and IG are employees of DNA-Technology JSC, Moscow; GL has nothing to disclose; SS has nothing to disclose; NV has nothing to disclose; OS has nothing to disclose; AG has nothing to disclose.

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