DOI: https://doi.org/10.2298/SARH211118013R
UDC: 615.2.015:575.1

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The *VKORC1* and *CYP2C9* gene variants as pharmacogenetic factors in acenocoumarol therapy in Serbian patients – consideration of hypersensitivity and resistance

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SUMMARY

Introduction/Objective Coumarin therapy represents one of the best models for applying pharmacogenetics. The contribution of factors influencing coumarin therapy can vary significantly between ethnic groups, which justifies conducting population-specific studies. The aim of this study was to analyze the influence of the most important genetic factors (*VKORC1* and *CYP2C9* genes) that affect coumarin therapy in patients from Serbia.

Methods A retrospective study involving 207 patients on acenocoumarol therapy was conducted. Genetic analyses were performed by direct sequencing. Influence on acenocoumarol dose of variants (*VKORC1*, *CYP2C9*2, CYP2C9*3*) causing hypersensitivity and *VKORC1* variants causing resistance to acenocoumarol were analyzed. Multiple regression analysis was used to design a mathematical model for predicting individual drug dosage based on clinical-demographic and genetic data.

Results The study confirmed significant influence of the analyzed genetic factors on acenocoumarol maintenance dose. We designed mathematical model for predicting individual acenocoumarol dose and its unadjusted R2 was 61.8. In the testing cohort, our model gave R2 value of 42.6 and showed better prediction in comparison with model given by other authors. In the analyzed patients, nine different variants in the *VKORC1* coding region were found. Among carriers of these variants 78% were completely resistant, and it was not possible to achieve therapeutic effect even with high doses of acenocoumarol.

Conclusions Population-specific model for prediction individual dose of acenocoumarol, may show advantages over protocols that are used in a generalized manner. Also, *VKORC1* variants which cause coumarin resistance should be considered when planning therapy.

Keywords: pharmacogenetics; coumarin derivatives; acenocoumarol; *VKORC1*; *CYP2C9*

INTRODUCTION

Coumarin derivatives or coumarins (warfarin, acenocoumarol, phenprocumon) are oral anticoagulants which act by inhibiting the synthesis of vitamin K-dependent clotting factors and they are widely prescribed for treatment and prevention of thrombosis [1]. Although coumarin derivatives are very effective on average, their use represents a great challenge in some patients and it is particularly notable during therapy initiation. It is a matter of narrow therapeutic window and inter-individual differences in drug dosage needed for achieving therapeutic effect (given as International Normalized Ratio – INR), as well as intra-individual differences in the required dose over time. As a result, patients require frequent control, but even with careful monitoring and titration towards a patient's maintenance dose, coumarin therapy is often subtherapeutic, or supratherapeutic [2, 3].

Pharmaceutical industry managed to launch new anticoagulant drugs, as alternative to coumarin derivatives, in the form of direct inhibitors of certain coagulation factors (thrombin or FX-a). Direct oral anticoagulants offer much more comfortable use due to therapeutic effects without large inter-individual fluctuations and due to no need to check INR values [4]. However, despite their benefits, new anticoagulants are not the right choice for all patients (e.g., patients with artificial valves) [5].

Significant possibilities for understanding and overcoming problems related to use of coumarin derivatives, have been presented by personalized medicine. It is previously established that patient's response to coumarins depends on several acquired factors such as age, dietary intake, intercurrent illness and other drugs [6, 7, 8]. Pharmacogenetic research has made the biggest contribution to understanding inter-individual differences related to therapeutic effects of coumarin. They have demonstrated that certain variants of gene influencing pharmacodynamic (*VKORC1*) and pharmacokinetic (*CYP2C9*) of coumarins have the biggest impact on therapeutic effects of these drugs.

Received • Примљено: November 18, 2021
Accepted • Прихваћено: January 23, 2022
Online first: January 25, 2022

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The *VKORC1* (Vitamin K epOxide Reductase Complex subunit 1) gene encodes subunit 1 of vitamin K epoxide reductase – the key enzyme of the vitamin K cycle and the pharmacological target of coumarins. A single nucleotide substitution *VKORC1*2* (c.-1639G>A; rs9923231) in the promoter region of the *VKORC1* gene results in a suppression of gene expression which leads to decreased production of the coumarin target. The *CYP2C9* gene expresses the enzyme cytochrome P450 2C9 that takes part in the hepatic metabolism of coumarins. Two variant alleles of this gene – *CYP2C9*2* (c.430C> T; rs1799853) and *CYP2C9*3* (c.1075A>C; rs1057910) – are associated with reduced enzyme activity, resulting in deficient clearance of coumarin derivatives [8, 9, 10]. It has been shown that the *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants are major genetic predictors of hypersensitivity to coumarins in Caucasians. Carriers of these allele variants need significantly lower dose, in comparison to patients who do not have these variants [8, 9]. Additionally, the variants in the coding region of the *VKORC1* gene are the main cause of coumarin resistance [9]. Several research groups worldwide presented the mathematical models for predicting individual dosage of coumarins. These models usually include clinical and demographic data as well as genetic factors associated with coumarin sensitivity, while genetic factors that cause resistance are usually omitted from these models [10, 11]. Further, it has been shown that the contribution of genetic and non-genetic factors affecting coumarin therapy may vary markedly between patients from different ethnic groups [12], which justifies conducting population-specific studies.

In this study, we set the goal to analyze the influence of major genetic factors influencing coumarin therapy, in patients from Serbia. Further, assuming that population-specific protocols may take advantage over protocols used in a generalized manner, we aimed to design a mathematical model for predicting individual drug dosage in the Serbian population based on clinical-demographic and genetic data (*VKORC1*2*, *CYP2C9*2*, *CYP2C9*3).* We also aimed to consider the possible reasons for improving pharmacogenetic strategies in coumarin administration by taking into account genetic factors that cause resistance.

METHODS

Patients

The study included patients registered in Anticoagulation Service for outpatient's treatment (the Blood Transfusion Institute of Serbia, Hemostasis Department) who were using acenocoumarol as anticoagulation therapy. Therapeutic INR value was 2–3**.** Indications for anticoagulation therapy were deep venous thrombosis, pulmonary embolism and arrhythmia. Additional criteria for including patients into the study were that they had to be the age of 18 and above. Excluded patients were those with liver or kidney dysfunction, malignant disease, as well as pregnant women and nursing mothers.

Laboratory testing and data collecting

Commercially available tests were used for standard laboratory testing. Sequencing of *VKORC1* coding region and determination of *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants were performed as previously described [13, 14]. Demographic, clinical and genetic data relevant to the study were taken from medical records existing for each patient. After data collection we did retrospective analysis of all the data for the patients included in the study. The research was conducted with the approval of the Ethical Committee of the Blood Transfusion Institute of Serbia and written consent of all the patients involved in the research.

Outcome and determinants

Mean stable acenocoumarol maintenance dose in mg/week, at the first stable period after initiation of anticoagulation therapy was used as the outcome measure. Stable maintenance dose was calculated from weekly doses that were unchanged over a minimum of three consecutive measurements of therapeutic INR. To develop prediction model, age (in years), height (in centimeters), weight (in kilograms), sex, use of amiodarone and genetic variants (*VKORC1*2*, *CYP2C9*2* and *CYP2C9*3*) are considered as determinants.

Statistical analysis

Demographic, clinical and genetic characteristics of the whole group of patients analyzed in this study are presented by descriptive statistics. Categorical variables are presented as numbers or percentages and continuous data are summarized as means and standard deviations. The normality of continuous variables was evaluated using the Kolmogorov–Smirnoff test. Allele frequencies were estimated by gene counting and departure from Hardy–Weinberg equilibrium (HW) was tested using the χ^2 test. Conjugated influence of genetic and non-genetic factors was investigated by multiple regression analysis. With the purpose of designing and testing mathematical equation i.e., model which would derive from multiple regression analysis, the patients with stable acenocoumarol maintenance dose (N = 200) were divided into two cohort – derivation cohort (N = 100) and testing cohort (N = 100) – on random basis. The differences between cohorts were tested using the χ^2 test for categorical variables and the Unpaired T test and Mann–Whitney U test for continuous variables. On the derivation cohort multiple regression analysis was applied in order to select predictors to be used for estimating the individual dose of acenocoumarol and to derive model for acenocoumarol dose prediction. The testing cohort was used for assessing the quality of the mathematical equation derived from multiple regression analysis. Also, we searched the literature for models which use similar parameters for acenocoumarol dosage prediction. These selected models proposed by other authors, were compared with model provided by our study. The coefficient of determination (R2) and the mean absolute

error (i.e., 95% confidence interval which this value takes) in the validation data set were our pre-fixed values for evaluating the designed model. For all statistical tests $p < 0.05$ was considered statistically significant.

RESULTS

General characteristics of patients

Overall, 207 patients were enrolled in the retrospective study and baseline characteristics of patients are shown in Table 1. The majority of subjects (N = 200) were patients on stabile anticoagulation therapy, i.e., in a therapeutic INR (2–3) for three months. The average maintenance dose for these patients was 18.8 mg/week. Based on the dose level, patients were divided into three groups: Low maintenance dose (< 7 mg/week), Medium maintenance dose (7–28 mg/week), High maintenance dose (> 28 mg/week). In minority of the anticoagulated patients (N = 7), it was not possible to reach therapeutic INR values, even with high doses of acenocoumarol (complete resistance). In these patients, antithrombotic therapy was continued without vitamin K antagonist by introducing direct anticoagulants.

Table 1. Demographic, clinical and genetic characteristics of analyzed patients

Characteristics (variable)	Entire group (N = 207)
Patients with achieved therapeutic INR range, N (%) Low maintenance dose, N (%) Medium maintenance dose, N (%) High maintenance dose, N (%)	200 (196.6) 43 (20.8) 127 (61.3) 30 (14.5)
Patients out of therapeutic INR range (complete resistance), N (%)	7 (3.4)
Sex (female/male)	82/125
Age (years); mean ± SD	60.46 ± 13.556
Dose (mg/week); mean ± SD	18.8 ± 11.045
Weight (kg); mean ± SD	85.09 ± 11.88
Height (cm); mean ± SD	174 ± 7.379
Amiodaron users; N (%)	15 (7.5)
Genotype; N (%)	
CYP2C9	
CYP2C9*1*1	143 (69)
CYP2C9*2*1	34 (16)
CYP2C9*2*2	3 (2)
CYP2C9*2*3	4 (2)
CYP2C9*3*1	23 (11)
HW-X2 test p-value	0.64
VKORC1	
VKORC1 *1*1	69 (33)
VKORC1 *1*2	89 (43)
VKORC1 *2*2	49 (24)
HW-X2 test p-value	0.06

INR – international normalized ratio; SD – standard deviation; N – number of patients; HW – Hardy–Weinberg equilibrium

Analysis of the *VKORC1* and *CYP2C9* variants related to sensitivity to acenocoumarol

In the group of 207 analyzed patients, 89 patients (43%) were heterozygotes and 49 patients (24%) who were homozygotes for the *VKORC1*2* variant. Also, there were 34 patients (16.4%) with C*2*1 genotype, three patients (1.45%) with C*2*2 genotype, four patients (1.93%) with C*2*3 genotype and 23 patients (11.1%) with C*3*1 genotype (Table 1). Based on these data, the frequencies of *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* alleles are 0.45, 0.11 and 0.065 respectively. Studied variant alleles were in HW equilibrium.

In the group of 207 subjects, 158 patients were carriers of at least one studied variant. In patients (N = 200) who were on stabile anticoagulation therapy, 157 patients had at least one variant associated with sensitivity to coumarins. The average maintenance dose of acenocoumarol for these patients was 16.29 mg/week and it significantly differed ($P < 0.000$) comparing to the average maintenance dose of 27.95 mg/week for patients who were *wild type* for all three analyzed variants.

Creating and testing of prediction model

To create a prediction model, which reflects complex and conjugated influence of genetic, demographic and clinical factors, we used the group of patients on stabile anticoagulation therapy (N = 200). The group was divided into two cohorts - the derivation cohort for creating prediction model and the testing cohort for its testing. 100 patients were randomly selected for each cohort. There were no statistically significant differences between the cohorts in terms of demographic and clinical characteristics, as well in terms of distribution of the studied alleles. HW equilibrium was satisfied in both general group of patients and individual cohorts (Table 2).

The logarithm of the maintenance dose value was used as a dependent variable. Multiple regression analysis was conducted on the derivation cohort. In addition to *VKORC1* and *CYP2C9* variants, age, weight and sex were identified as significant predictors of acenocoumarol dose, and unadjusted R2 was 61.8. Mathematical equation for prediction of acenocoumarol maintenance dose was designed based on the output of linear regression: dose (mg/week) = $10^{(1.39 + 0.065\ (\text{for female}) - 0.006\times\text{age} + 0.004\times\text{weight} - 0.192\ (\text{for C*1*2}) - 0.298\ (\text{for C*2*2}) - 0.269(\text{for C*2*3}) - 0.188\ (\text{for C*1*3}) - 0.11\ (\text{for V*1*2}) - 0.288\ (\text{for V*2*2}))}$.

The equation was tested on the independent group of patients - testing cohort, and compared with mathematical models for prediction of acenocoumarol dose given by highly cited model for Dutch population, given by van Schie et al. [10], and model for Greek population, given by Markatos et al. [15]. In the case of the equation given by Van She et al. [10], we also applied the mathematical conversion, given by the authors, which is needed to compare their formula with other models. Our model gave R2 value 42.6, and showed better prediction in comparison with model given by van Schie et al. [10] which value of R2 was 37.8. Also, there was a slight advantage to our model

Table 2. Demographic, clinical and genetic characteristics of patients in the derivation and the testing cohort

Characteristics (variable)	Derivation cohort (N = 100)	Testing cohort (N = 100)	P-value (derivation cohort vs. testing cohort)
Gender (female/male)	39/61	40/60	0.885*
Age (years) mean ± SD	61.64 ± 12. 498	59.27 ± 14.504	0.317 **
Dose (mg/week) mean ± SD	18.86 ± 9.68	18.74 ± 12.306	0.402 **
Weight (kg) mean ± SD	84.32 ± 12.49	85.86 ± 11	0.361 ***
Height (cm) mean ± SD	173.87 ± 7.209	174.33 ± 7.574	0.707 **
Amiodaron users N (%)	6 (6)	9 (9)	0.421 *
Genetic characteristics			
CYP2C9 genotypes N (%)			
*CYP2C9*1*1	70 (70)	66 (66)	0.544
*CYP2C9*2*1	16 (16)	18 (18)	0.706
*CYP2C9*2*2	1 (1)	2 (2)	0.561
*CYP2C9*2*3	3 (3)	1 (1)	0.312
CYP2C9 *3*1	10 (10)	13 (13)	0.506
HW-X2 test p-value	0.460	0.724	/
VKORC1 genotypes N (%)			
VKORC1 *1*1	31 (31)	32 (32)	0.879
VKORC1 *1*2	46 (46)	42 (42)	0.569
VKORC1 *2*2	23 (23)	26 (26)	0.622
HW-X2 test p-value	0.4585	0.116	/

*χ^2 test; **Mann–Whitney U test; ***Unpaired T test; SD – standard deviation; N – number of patients; HW – Hardy–Weinberg equilibrium

Table 3. Comparison of algorithms for acenocoumarol dose prediction

Algorithm	Mean weekly dose CI 95% SD	Mean absolute error CI 95%	Unadjusted R2 of authors original algorithm (%)	R2 in our testing cohort (%)
Van Sche et al. [10]	18.17 17.09–19.28 5.72	7.18 5.95–8.58	53	37.8
Markatos et al. [15]	17.77 16.52–19.22 7.01	6.77 5.53–8.14	55	41.1
Our algorithm	17.90 16.50–19.38 7.13	6.83 5.66–8.15	61.8	42.6
Real mean dose	18.74 16.40–21.26 12.31			

CI – concordance interval; SD – standard deviation

over model given by Markatos et al. [15] which R2 in our testing cohort value was 41.1 (Table 3).

Analysis of the *VKORC1* variants related to resistance to acenocoumarol

The sequencing of *VKORC1* exons was performed in order to analyze the frequency and distribution of variants causing resistance to acenocoumarol. In the analyzed group of 207 patients, nine patients with different variants of the *VKORC1* coding region were found. Detected variants and resulting amino acid substitutes with their positions in the protein are given in Table 4. Seven of nine variants detected in the *VKORC1* coding region were found in patients who had complete resistance to acenocoumarol. Two variants have been detected in patients with high maintenance (N = 30) doses of acenocoumarol. No variants in the coding region of the *VKORC1* gene were detected in patients with medium (N = 127) and low doses (N = 43).

DISSCUSION

Coumarin derivatives are still the pivot of anticoagulant therapy in Serbia. However, pharmacogenetic studies considering *VKORC1* and *CYP2C9* gene, has been focused only to therapy of smaller group of elderly patients [13]. Until now, there have not been studies examining pharmacogenetic factors in more complex manner, which would enable predicting response to anticoagulant therapy and formulating the model for using anticoagulant therapy in our population. With regard to the impact on therapeutic regiment of acenocoumarol, this study investigates two most important pharmacogenetic factors – *VKORC1* and *CYP2C9*. *VKORC1* gene dominates with its pharmacogenetic potential exhibiting variants

Table 4. Nucleotide substitution in coding region of *VKORC1* gene detected in analyzed patients

Nucleotide substitution	Amino acid substitution	Location of amino acid substitution	Effect on acenocoumarol therapy	Variants associated with sensitivity
c.76G > C	Ala26Pro	Entirely conserved place in vertebrates; the interface between the first TM helix and the ER luminal domain	Complete resistance*	Not detected
c.84C > T	His28Gln	Coumarin binding interface	Moderate resistance	Not detected
c.106G > T	Asp36Tyr	The outer surface loop	Moderate resistance	Carrier of the *CYP2C9*2*
c.160G > C	Val54leu	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.175T > C	Trp59Arg	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.176G > T	Trp59leu	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.177G > T	Trp59Cys	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.383T > G	Leu128Arg	The first TM helix; entirely conserved place in vertebrates	Complete resistance*	Not detected
c.368T > A	Ile123Asn	The end of TM3, adjacent to the third putative coumarins binding interface	Complete resistance*	Not detected

TM helix – transmembrane helix; ER – endoplasmic reticulum; * therapy aborted

responsible for hypersensitivity and resistance to the drugs.

As expected, the study confirmed significant influence of examined genetic factors on maintenance dose of acenocoumarol. The frequency of the *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants in analyzed sample of Serbian population has been shown as high. Over 60% of patients in the entire group were carriers of the *VKORC1*2* variant allele. Additionally, almost 80% of patients had at least one of the studied variant alleles and the average weekly dosage of acenocoumarol in these patients was almost twice as low comparing to dosage given to patients who were *wild type* for all three variants. This is significant for medical practice considering proved predisposition to hypersensitivity in the carriers of abovementioned variants, and keeping in mind that both professional guidelines and producers of acenocoumarol (and other coumarins) demand caution when treating carriers of these variants [9, 12].

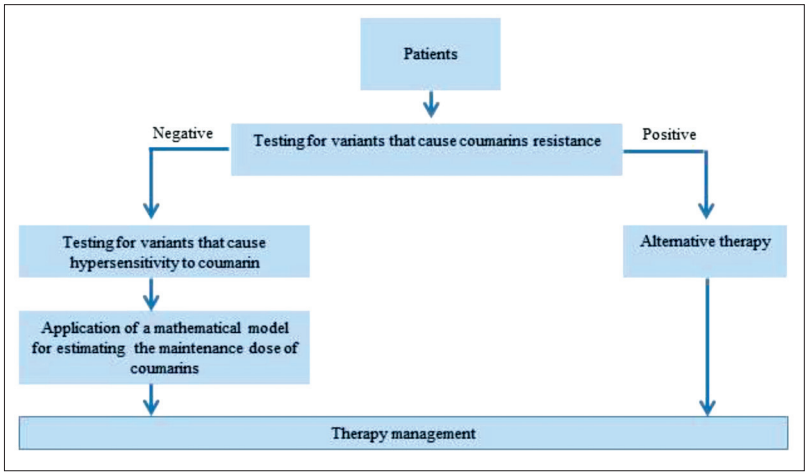

Figure 1. Proposed strategy in the management of anticoagulant therapy, based on pharmacogenetic testing

The results of pharmacogenetic analyses, along with clinical and demographic data, were used for designing and testing mathematical model for predicting individual maintenance dose of acenocoumarol. As expected, in the resulting model, not only did *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants prove to be predictive factors, but also sex, age and weight. In this study, influence of antiarrhythmic drug amiodarone did not show to have significant influence on maintenance dose of acenocoumarol, which is in correlation with predictive model given by other authors, too [15]. On the other hand, there are studies showing amiodarone as a significant factor for assessing maintenance dose of acenocoumarol as well as of phenprocoumon [10]. Such different conclusions may come from factors influencing both the effects of coumarins, and bioavailability and effects of amiodarone. Thus, it has been shown that bioavailability and effect of amiodarone can be modulated by the dietary intake [16]. In addition, there is evidence that certain probiotics can significantly influence pharmacokinetics of this antiarrhythmic [17]. Very often these factors (such as food ingredients) are one of the key differences between populations.

The comparison drawn between prediction model for Serbian population and other algorithms we tested indicates that our model had better prediction than the model given for Dutch population by van Sche et al. [10]. Also, our model had just a slight advantage over the model for Greek population by Markatos et al. [15]. One explanation for such outcome might be geography, i.e., both Greek and Serbian population belongs to Southeast Europe, unlike Dutch population which belongs to Western Europe.

The *VKORC1* variants causing resistance, detected in our study group, are also described by other authors. Resulting amino acid substitutes and their positions in the protein, point to functional significance of these variants.

Change His28Gln is detected in a patient with achieved therapeutic INR value (maintenance dose of acenocoumarol was 60 mg per week). In fact, His28Gln is a change with milder resistance effect, which had been previously elaborated by Czogalla et al. [18]. Change Asp36Tyr is listed as the most often detected substitution in patients with resistance to coumarin. The study conducted by Watzka et al. [19] concerning *VKORC1* variants causing acenocoumarol resistance, showed that this variant represented a quarter of all changes found in the *VKORC1* enzyme. In the majority of patients who were carriers of the Asp36Tyr substitution, the therapeutic value of INR was achieved [19]. In our study change Asp36Tyr was detected in one patient and therapeutic INR was reached with 57 mg of acenocoumarol per week. Substitutions Ala26Pro, Val54Leu, Trp59Arg, Trp59Leu Trp59Cys, Ile123Asn and Leu128Arg are situated in conserved regions of VKORC1 enzyme and their presence leads to significant changes in VKORC1 function. The potential of these substitutions to induce coumarin resistance has been confirmed by a number of authors [9, 18, 19].

In terms of variants which causing resistance, it was not possible to perform appropriate statistical analyses related to probability theory, due to the sample size. Descriptive analysis showed that all carriers of detected *VKORC1* variants showed resistance to acenocoumarol; 75% of them had complete resistance and it was necessary to introduce a different kind of anticoagulant. This is a significant piece of data since timely recognition of patients predisposed to resistance to the drug offers possibility to avoid the risks of trial-and-error method.

Pharmacogenetic algorithms, which are proposed for coumarin therapy, contains genetic variants that are associated with sensitivity but not with drug resistance. Thus, variants causing resistance are being neglected in pharmacogenetic protocols and they are omitted in prospective study or trials. It can be assumed that this practice leaves room for outliers and influences final interpretation of results. That may be one of the reasons that the use of pharmacogenetic algorithms, very often, does not give an advantage over traditional treatment [20, 21]. In accordance

with the above, improved strategy in the management of anticoagulant therapy can be presented as in Figure 1.

Study weakness

This study was based on an analysis of variants of only two genes. Also, in this context, they can be mentioned limited number of patients, the impossibility of conducting a prospective study or the trial study.

CONCLUSIONS

In conclusion, our results suggest that population-specific pharmacogenetic model shows advantages over models that would be used in a generalized manner. Additionally, protocols for the use of coumarins, should not have only mathematical formulas based on genetics factors related to sensitivity, but also testing to *VKORC1* variants causing resistance.

ACKNOWLEDGMENT

This work was supported by the Ministry of Education, Science and Technological Development of Republic of Serbia (No. 173008).

Conflict of interest: None declared.

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Варијанте гена *VKORC1* и *CYP2C9* као фармакогенетички фактори у терапији аценокумаролом код болесника у Србији – разматрање преосетљивости и резистенције

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САЖЕТАК

Увод/Циљ Терапија кумаринима представља један од најбољих модела за примену фармакогенетике. Допринос фактора који утичу на терапију кумаринима може значајно да варира између етничких група, што оправдава спровођење студија специфичних за популацију.

Циљ ове студије је био да се анализира утицај најважнијих генетичких фактора (гени *VKORC1* и *CYP2C9*) који утичу на терапију кумаринима код болесника из Србије.

Методе Спроведена је ретроспективна студија која је обухватила 207 болесника на терапији аценокумаролом. Генетичке анализе су вршене директним секвенцирањем. Анализиран је утицај на дозу аценокумарола варијанти (*VKORC1*2*, *CYP2C9*2*, *CYP2C9*3*) које изазивају преосетљивост и варијанти гена *VKORC1* које изазивају резистенцију на кумарине. Вишеструка регресиона анализа је коришћена у циљу дизајнирања математичког модела за предвиђање индивидуалне дозе лека на основу клиничко-демографских и генетичких података.

Резултати Студија је потврдила значајан утицај анализираних генетичких фактора на одржавање дозе аценокумарола. Дизајниран је математички модел за предвиђање индивидуалне дозе аценокумарола и његов некориговани *R*2 је био 61,8. Приликом тестирања, наш модел је дао *R*2 вредност од 42,6 и показао боље предвиђање у поређењу са моделом који су дали други аутори. Код анализираних болесника пронађено је девет различитих варијанти у кодирајућем региону гена *VKORC1*. Међу носиоцима ових варијанти 78% је било потпуно резистентно, те није било могуће постићи терапеутски ефекат чак ни са високим дозама аценокумарола.

Закључци Популациони модел за предвиђање индивидуалне дозе аценокумарола може показати предности у односу на моделе који се користе на генерализован начин. Такође, *VKORC1* варијанте које изазивају резистенцију на кумарин треба узети у обзир приликом планирања терапије.

Кључне речи: фармакогенетика; деривати кумарина; аценокумарол; *VKORC1*; *CYP2C9*