New Pharmacogenetic Markers to Predict the Risk of Bleeding During Taking of Direct Oral Anticoagulants

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Aim. To search for new pharmacogenetic biomarkers of bleeding risk in patients taking rivaroxaban and dabigatran for different indications: atrial fibrillation, endoprosthesis of large joints of lower limbs.
Material and methods. The study enrolled 29 patients (17 patients received dabigatran and 12 –rivaroxaban), who had hemorrhagic complications during taking direct oral anticoagulants. To find new pharmacogenetic biomarkers of bleeding risk, a next generation sequencing (NGS) was performed for selected candidate genes.
Results. Among the patients with bleeding who received dabigatran, 13 variants of the nucleotide sequence showed statistically significant deviation from the population values: 11 in the *CES1* gene and 2 in the *ABCB1* gene. Among the patients with bleeding who received rivaroxaban, 7 variants of nucleotide sequence showed significant deviation: 4 in the *ABCG2* gene, 2 in the *CYP3A4* gene, and 1 in the *ABCB1* gene.
Conclusion. The identified in this study polymorphisms of candidate genes *ABCB1, ABCG2, CES1, CYP3A4* were associated with the risk of bleeding in patients taking rivaroxaban and dabigatran. It makes an important contribution to the pharmacogenetics of direct oral anticoagulants and require additional assessment of clinical significance in further studies.

Keywords: dabigatran, rivaroxaban, pharmacogenetics, direct oral anticoagulants, sequencing, personalized medicine.

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The direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, edoxaban) are now widely used for thromboembolism prevention in patients with non-valvular atrial fibrillation (AF), after knee and hip replacement and for prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). In the USA since 2011 to 2014 prescription of rivaroxaban increased from 0.13% to 13.87%, and dabigatran from 1.3% to 7.6% [1]. The proportion of DOACs among oral anticoagulants in 2017-2018 was 56.5% and 31% in the UK and the USA, respectively [2,3]. In 2018 rivaroxaban and apixaban were among the top 10 best-selling medicines in the U.S.: 10th and 2nd place, respectively [4].

The increase in DOACs use which have a number of benefits in comparison with warfarin (faster onset of action, no need for routine control of pharmacodynamic response, predictable pharmacokinetics, fixed dosage regimen etc.) is associated with the most common adverse event – bleeding including some of them requiring emergency medical care [5]. For example, in the UK, each increase in DOACs prescription by 10% in routine general practitioners practice results in 0.9% increase in hemorrhagic events [5]. At the same time, with the begining of DOACs use 4,929 additional cases of emergency hospitalization due to hemorrhagic events during anticoagulant therapy were registered in this country between 2011 and 2016 [5].

Different clinical and demographic factors (age, renal function impairment, race and ethnicity, gender, smoking, drug interactions, diet, etc.) as well as genetic factors (polymorphism of genes encoding cytochrome P-450 isoenzymes and drug transporters, etc.) contribute to the variability of pharmacological response to DOACs. At the same time, despite the rapid growth of DOACs prescription and the increase in hemorrhagic events during therapy, peculiarities of DOACs pharmacogenetics remain insufficiently studied [6]. Today, there is a limited number of pharmacogenetic studies of the relationship of gene polymorphism of the drug transport system and drug metabolism (ADME) with a response to DOACs: single-nucleotide polymorphisms of *CES1* and *ABCB1* genes affecting pharmacokinetic parameters and clinical outcomes during dabigatran therapy and single-nucleotide polymorphisms of *ABCB1* gene affecting pharmacokinetic parameters of rivaroxaban and apixaban have been detected [7]. However, there is a significant lack of data on the search for new genetic biomarkers through genome sequencing (exom, full genome) or individual candidate genes in patients with an unsatisfactory response and hemorrhagic events due to DOACs.

The aim of the present study was to search for new pharmacogenetic biomarkers of bleeding risk in patients with atrial fibrillation or after hip and knee replacement taking rivaroxaban and dabigatran.

Material and methods

Written informed consent to participate in the study has been received from all participants. The study was approved by the local Ethical committee of Russian Medical Academy of Continuous Professional Education.

Patients

The study included 29 patients (17 patients received dabigatran and 12 patients – rivaroxaban) from real clinical practice with bleedings classified as 2 or 3 type on BARC scale (Bleeding Academic Research Consortium). Selection of participants was carried out in I.M. Sechenov First Moscow State Medical University (Sechenov University) and Saratov State Medical University named after V.I. Razumovsky. Men accounted for 35.2% in dabigatran group and 75% in rivaroxaban group. The median age was 72.5 [45;86] and 71 [40;87] years in dabigatran and rivaroxaban groups, respectively. Demographic, clinical and laboratory features are presented in Table 1.

Justification for selecting candidate genes for next-generation sequencing (NGS)

The initial sample of patients was divided into two groups: a) patients who received dabigatran (n=17) b) patients who received rivaroxaban (n=12). In each group the search for potentially significant variants in target genes was done. According to the literature search on the specialized resource PharmGKB [8] and known pharmacokinetic features of the DOACs from Summary of product characteristics [9]

Table 1. Characteristics of the study participants

Parameter	Dabigatran (n=17)	Rivaroxaban (n=12)
Men, n (%)	6 (35.2)	9 (75)
Age, years	72.5 [45;86]	71 [40;87]
DOAC serum concentration, ng/ml	144.3 [36;800]	60.1 [24;243]
CHA_2DS_2VASc score, points	4 [3;7]	4.5 [3;8]
HAS-BLED score, points	1 [0;2]	3 [1;6]
Hemoglobin, g/l	137 [99;167]	125.5 [73;161]
Platelets, 10^9/l	184 [116;246]	No data available
Thrombocytopenia, n (%)	2 (11.7)	0
GFR, ml/min/1.73 m^2	53.5 [31;101]	50.5 [16;90]
Dose of DOAC, mg/day	110 [110;220]	15 [10;15]
Atrial fibrillation, n (%)	12 (70.6)	10 (83.3)
Hip or knee replacement, n (%)	5 (29.4)	2 (16.7)

Data are presented as Me [25%;75%] or n (%)

DOAC – direct oral anticoagulants, GFR – glomerular filtration rate

ABCB1 and *CES1* for dabigatran, *ABCB1*, *ABCG2* and *CYP3A4* for rivaroxaban were selected to look for novel pharmacogenetic markers. *ABCB1* gene encodes P-glycoprotein or multiple drug resistance protein, a substrate for which are both rivaroxaban and dabigatran [10]. Rivaroxaban's pharmacokinetics may also be affected by another *ABCG2* transporter that encodes the breast cancer resistance protein (BCRP) [10]. Gene *CES1* encodes carboxylesterase-1, which participates in metabolism of dabigatran to form dabigatran etaxylate. Finally, the gene *CYP3A4*, encodes the isoenzyme of cytochrome system P-450 – *CYP3A4*, a substrate for which is rivaroxaban [10].

DNA extraction. DNA was extracted from whole peripheral venous blood samples by selective prescription using high concentrations of salts ("salting-out").

Sequencing. Mutations in patients were screened by high-performance semiconductor parallel DNA sequencing using Ion S5 (Thermo Fisher). In the process of sample preparation we used the standard protocol of preparation byAmpliSeq libraries (Thermo Fisher) with the help of Ion AmpliSeq Library Kit 2.0 reagents and user panel of primers, which includes exons and adjacent intron areas of *ABCB1*, *ABCG2*, *CES1*, *CYP3A4* genes, as well as their 5' and 3' non-coding areas.

Analysis of sequencing results was carried out using the following software:

1) Torrent Suite consisted of (1.1. Base Caller for primary basic analysis of sequencing results; 1.2. TMAP (Torrent Mapping Alignment Program) for alignment of reading sequences with reference genome (as which NCBI 37/hg19 assembly was used); 1.3. Variation Caller for identification of genetic variants);

2) ANNOVAR (annotation of the functional value of genetic variants, filtration of known polymorphisms using the GnomAD database);

3) IGV (Integrative Genomic Viewer) for expert filtration of sequencing artifacts and sequence alignment results in which mutations are detected by automatic analysis tools.

To determine the potentially significant variants for each found variant, the occurrence in the investigated group was compared with the occurrence in the sample of 15708 complete genomes of healthy people, separated by NGS method, from the GnomAD database [11]. The p-value was calculated using the continuity corrected χ-square (Statistica program), FDR correction was used as a multiple test correction.

Table 2. Variants, the frequency of which differs significantly among patients with bleeding events during dabigatran therapy and in the general population

Gene	Reference variant	Alternative variant	Substitution type, location	Rs	Frequency in the studied sample	Frequency in GnomAD
ABCB1	A	G	Lower cis-regulating area	*rs41297348*	0.0555	0.0001
ABCB1	T	C	Exonic, non-synonymous	*rs9282564*	0.3888	0.0903
CES1	T	C	Exonic, non-synonymous	*rs3826193*	0.7222	0.2468
CES1	T	-	On the 5'-non-transmitted area	*rs761128900*	0.1111	0.0016
CES1	T	C	Intronic	*rs375970897*	0.0555	0.0
CES1	C	T	Exonic, non-synonymous	*rs3826192*	0.7777	03202
CES1	G	A	Exonic, synonymous	*rs3826191*	0.7777	0.3298
CES1	C	G	Exonic, synonymous	*rs3826194*	0.7777	0.3548
CES1	C	T	Exonic, non-synonymous	*rs2307240*	0.2222	0.0434
CES1	A	G	Intronic	*rs62028646*	0.7777	0.4055
CES1	G	A	Exonic, non-synonymous	*rs62028647*	0.7777	0.4134
CES1	T	C	Exonic, synonymous	*rs74019278*	0.7777	0.4178
CES1	T	C	Exonic, synonymous	*rs76828834*	0.7777	0.4183

Measuring of rivaroxaban and dabigatran plasma concentrations

Determination of rivaroxaban and dabigatran plasma concentration was carried out by high-performance liquid chromatography (HPLC) with mass spectrometric detection. Samples were analyzed on the Agilent 1200 liquid chromatograph (consisting of a four-channel pump, mobile phase degasser, chromatographic column thermostat). The Agilent Extend-C18 column (length 100 mm; inner diameter 2.1 mm; grain 3.5 μm) was used. The separation was performed at a column temperature of 40°C. Moving phase: solution "A" (50 ml 0.1 M ammonium acetate solution and 5 ml formic acid solution were diluted with deionized water to a total volume of 1 litre) and solution "B" (50 ml 0.1 M ammonium acetate solution and 5 ml formic acid solution were diluted with acetonitrile to a total volume of 1 litre).The chromatographic separation was performed in the isocratic elution mode with the ratio of components "A":"B" 70:30. The flow rate of the mobile phase was 0.3 ml/min. The volume of the introduced sample was 10 μl. The analysis was carried out during 7 min.

We used a mass spectrometer (triple quadrupole type) Agilent Triple Quad LC/MS 6410 with electrospray ionization in positive ionization mode. Registration of rivaroxaban spectra was performed in the mode of multiple molecular reactions. Sprayer gas pressure 35 psi. Drying gas volume speed 11 l/min, temperature 350°C. The value of the fragmentation voltage was 135 V, the voltage in the impact cell was 25 V. The sample preparation was performed by the deposition of plasma proteins. The plasma samples were defrosted at room temperature. Then 100 μl of plasma was transferred to Eppendorf type tubes, 250 μl of methanol mixture with 0.1% hydrochloric acid HCl was added in 9:1 ratio, stirred on Vortex shaker, left for 10 minutes and stirred again. The samples were then centrifuged for 10 min at 10,000 rpm. The supernatant layer was transferred to a chromatographic vial and placed on a chromatograph autosampler.

Results

Dabigatran

In dabigatran group of patients with bleeding events statistically significant deviation from population values was shown by 13 variants of nucleotide sequence (table 2). Among the 11 significant substitutions found for the *CES1* gene, 8 *(rs3826193, rs761128900, rs3826192, rs3826191, rs3826194, rs2307240, rs62028647, rs74019278, rs76828834)* are in the exonic area. At the same

time, 4 of them *(rs3826193, rs3826192, rs2307240, rs62028647)* lie in the functionally significant area and are non-synonymous (i.e. they lead to the change in amino acid sequence) and 4 *(rs3826191, rs3826194, rs74019278, rs76828834)* are synonymous (i.e. they do not lead to the change in amino acid sequence). Of the remaining variants of the nucleotide sequence found in the *CES1* gene, 2 *(rs375970897, rs62028646)* belong to the intronic region and 1 to the 5'-nontranslated region *(rs761128900)*. Among the found significant substitutions for the *ABCB1* gene, 1 *(rs9282564)* is in the exonic region and is not synonymous; another 1 *(rs41297348)* substitution is in the underlying cis-regulating region.

Rivaroxaban

In patients received rivaroxaban with bleeding events significant deviations showed 7 variants of nucleotide sequence: 4 in *ABCG2* gene, 2 in *CYP3A4* gene and 1 in *ABCB1* gene (Table 3).

Among the 4 significant substitutions found for the *ABCG2* gene, one *(rs34783571)* is in the exonic region and is not synonymous. Of the remaining substitutions for the gene *ABCG2*, 1 *(rs2231157)* is in the intronic region and one by one is in the 5'-nontranslated region *(rs55927234)* and 3'- nontranslated region *(rs546230660)*. The variants showing significant deviations from the population frequencies in the genes *ABCB1 (rs531438597)* and *CYP3A4 (rs55808838)* are in the intronic region.

Tables 2 and 3 also show the carrier frequencies of the found variants in the present sample of patients with bleedings on dabigatran or rivaroxaban treatment and in general population. The predictive significance (increased risk of bleeding or protective role) of the found variants will be clarified in future studies on a larger sample of patients with a comparison of the obtained data with patients of similar groups without bleeding.

Discussion

Patients with bleeding events on DOACs (dabigatran and rivaroxaban) were included in this study. Among patients receiving dabigatran (110 and 220 mg two times a day), only 4 (23.5%) of 17 patients had minimum equilibrium plasma concentrations of the drug exceeding the previously described therapeutic limits [12]. Among patients taking rivaroxaban (10-20 mg once a day), 2 (16.6%) ones had a level of the minimum equilibrium plasma concentration of the drug above the previously described therapeutic limits. The data obtained may indicate that the "gold standard" – assessment of DOAC concentration is not an ideal prognostic factor of bleeding risk for patients taking DOACs; and therefore studies for additional markers of bleeding for dabigatran and rivaroxaban are required.

As mentioned above, dabigatran is a substrate of P-glycoprotein encoded with the *ABCB1* gene. In addition, hepatic carboxylesterase-1 (*CES1*), encoded by the *CES1* gene plays an important role in the pharmacokinetics of dabigatran, under the influence of which dabigatran metabolite M2 is converted into the active form of the drug, dabigatran etexilate. [13]. Several polymorphic variants of the *CES1* gene

Table 3. Parameters of longitudinal left ventricular deformation before and after CABG, depending on the preoperative approach

Gene	Reference variant	Alternative variant	Substitution type, location	Rs	Frequency in the studied sample	Frequency in GnomAD
ABCB1	A	-	Intronic	*rs531438597*	0,0833	0,0005
ABCG2	A	G	On the 3'-non-transmitted area	*rs546230660*	0,0833	0,0003
ABCG2	C	T	Exonic, non-synonymous	*rs34783571*	0,0833	0,0019
ABCG2	A	G	Intronic	*rs2231157*	0,7500	0,335
ABCG2	G	C	On the 5'-non-transmitted area	*rs55927234*	0,0833	0,0026
CYP3A4	C	T	Intronic	No data available	0,0833	No data available
CYP3A4	C	T	Intronic	*rs55808838*	0,0833	0,0015

associated with lower dabigatran plasma concentrations and lower risk of bleedings have been identified in earlier studies, including full genome association studies [14]. For example, the carriage of minor alleles by the polymorphic marker *rs2244613* of the *CES1* gene may be associated with lower dabigatran concentrations in plasma and lower risk of bleeding events on dabigatran [14]. Another single-nucleotide polymorphism of the same *rs8192935* gene demonstrated association with minimum and maximum dabigatran concentration, but did not affect the risk of bleedings [14,15]. The association with reduction of activation rate of dabigatran is shown also for polymorphic marker *rs71647871* of *CES1* gene [13]. Single-nucleotide polymorphisms *rs4148738*, *rs1045642* and *rs2032582* of the *ABCB1* gene, which have been associated with the dabigatran plasma concentration and the risk of bleeding on dabigatran should be highlighted [14,16,17]. At the same time, the variants identified in this study have not been previously described as associated with the risk of bleeding during therapy with dabigatran. This requires investigating the clinical relevance of the identified variants in larger studies. Moreover, the polymorphic variant *rs62028647* has shown a strong non-equilibrium linkage with previously well described [18] variant *rs2244613*, and these variants can be allocated as haplotype.

The polymorphism of *ABCB1*, *ABCG2* genes encoding the efflux transporters, and the polymorphism of *CYP3A4* gene encoding the eponymous isoenzyme of cytochrome P-450 system, may have a significant impact on the pharmacokinetics of rivaroxaban and the bleeding risk on rivaroxaban. Previously published studies have described 4 single-nucleotide polymorphisms of the *ABCB1* gene (*rs2032582*, *rs1045642*, *rs4148738*, *rs1128503*), which may be associated (mainly in haplotype) with higher plasma concentrations of rivaroxaban and, consequently, higher risk of bleeding events [17,19,20]. Some allelic single-nucleotide polymorphisms of *ABCG2* and *CYP3A4* genes, which affect significantly the pharmacokinetic features of rivaroxaban and the risk of bleeding during this treatment, are not described. The polymorphic markers identified in this study for the *ABCB1, ABCG2* and *CYP3A4* genes were not previously described as associated with the risk of bleeding during rivaroxaban therapy, which also requires an assessment of their clinical significance in larger studies.

Study limitations

The used NGS approach has some technological features; the variants selected according to the NGS results in subsequent studies will be confirmed by classical sequencing using the Senger method after the accumulation of data in larger samples. It should also be noted that the different size of the compared samples introduces additional statistical flaws and errors. Thus, the variants lying at the distribution edges of the smaller sample have a greater representation for their group and, accordingly, may show false significance. This points to the need to confirm the significance of the identified substitutions by comparison with a comparable control sample.

Conclusion

The polymorphic variants of candidate genes *ABCB1, ABCG2, CES1, CYP3A4* identified in this study, associated with the risk of bleeding during rivaroxaban or dabigatran treatment, make an important contribution to the pharmacogenetic study of DOACs and require additional assessment of clinical significance in larger studies.

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