PECULIARITIES OF DABIGATRAN PHARMACOGENETICS: LITERATURE REVIEW

A.O.Rubanenko, O.A.Rubanenko, Yu.V.Shchukin
Federal State Budgetary Educational Institution of Higher Education «Samara State Medical University»
of the Ministry of Healthcare of the Russian Federation, Samara, 89 Chapaevskaya str.

Dabigatran is highly effective oral anticoagulant used in patients with atrial fibrillation, venous thrombosis, pulmonary embolism, orthopedic surgery. The most important role in activation and transport of dabigatran play hepatic carboxylesterase-1 (CES-1) and P-glycoprotein. To date were studied different polymorphisms that affect the pharmacokinetics of dabigatran such as rs2244613 (C > A), rs8192935 (T > C) и rs71647871 (G > A), rs1128503 (1236 C > T), rs2032582 (2677 G > T), rs1045642 (3435 C > T) и rs4148738 (G > A) and others. At the same time, there is no need of dabigatran pharmacogenetics testing in routine care. On the other side, existing literature data is often controversial, that's why future studies are needed to answer the above-mentioned question.

A.O.Rubanenko - ORCID ID 0000-0002-3996-4689, O.A.Rubanenko - ORCID ID 0000-0001-9351-6177, Yu.V.Shchukin - ORCID ID 0000-0003-0387-8356

Dabigatran is known to be a direct oral anticoagulant whose mechanism of action is limited to direct inhibition of the coagulation factor thrombin-IIa [1]. This drug was developed primarily as an alternative to the indirect anticoagulant warfarin because numerous shortcomings of the latter made it difficult to use it in clinical practice. Dabigatran was first approved in Europe, then in 2010 in the United States and subsequently in Russia for the prevention of stroke in patients with atrial fibrillation (AF) [2]. Since then, it has been used in patients with deep vein thrombosis, pulmonary embolism, and in orthopedics [3, 4]. The advantages of dabigatran include good tolerability, ease of use, effective anticoagulant activity, predictable pharmacokinetics, and no need for routine coagulation monitoring during administration [1, 3, 5]. However, there is now evidence of the pharmacokinetics and pharmacodynamics of this drug in various patients who may present with thrombosis or hemorrhage in clinical practice [6-8].

The aim of this review was to evaluate the impact of different genetic polymorphisms on the pharmacodynamics and pharmacokinetics of dabigatran.

DABIGATRAN PHARMACODYNAMICS AND PHARMACOKINETICS

Dabigatran is known to be administered as a prodrug, dabigatran etexilate, with a bioavailability of about 7% [9]. Dabigatran etexilate is a substrate for the transport molecule P-glycoprotein and can therefore be combined with inducers (e.g., rifampicin, antiretroviral drugs, carbamazepine, etc.) as well as inhibitors (e.g., cyclosporine, clarithromycin, dronedarone, amiodarone, verapam-

il, ticagrelor, etc.) of this molecule, thereby contributing to a decrease or increase in the plasma concentration of this drug, respectively [10]. In the latter case, the risk of bleeding may increase with dabigatran [11]. For example, in a study by M.Bernier et al. (2019), bleeding occurred in 30.4% of patients taking dabigatran together with P-glycoprotein inhibitors, compared with 8.6% of patients not taking the aforementioned drugs [12]. Therefore, caution should be exercised when combining dabigatran with the above-mentioned drugs, and in some cases, it is even contraindicated, e.g., in patients receiving cyclosporine, dronedarone, intraconazole, ketoconazole for systemic use, and tacrolimus [11, 13]. Dabigatran etexilate is activated by intestinal (*CES2*) and hepatic (*CES1*) carboxylesterase to form short-lived metabolites, BIBR 951 and BIBR 1087 [8, 10]. The aforementioned metabolites are hydrolyzed by hepatic carboxylesterase *CES1* in hepatocytes to form dabigatran, the active drug [4, 10, 14, 15]. The formation of dabigatran from the prodrug is more dependent on *CES1* [8]. At the same time, it should be noted that activation of *CES2* can compensate for *CES1* deficiency in patients. Dabigatran has a low plasma protein binding capacity of 35% [10, 16], regardless of its concentration, so it can be excreted by hemodialysis. Dabigatran is partially conjugated with active glucuronic acid to form four isomers of pharmacologically active glucuronides [15, 17]. Therefore, the total plasma concentration of this drug includes free and glucuronide-containing dabigatran and peaks after approximately 1.5 hours [17]. The half-life of dabigatran is relatively long, ranging from 12-17 hours [9]. This drug is not metabo-

lized by cytochrome P450 and therefore has no effect on it except at concentrations above the therapeutic range [9, 16]. In addition, dabigatran does not interact with drugs metabolized by the above system [17]. The drug is excreted mainly through the kidneys by 80-90% [10].

DABIGATRAN PHARMACOGENETICS

Genetic polymorphisms of *CES1* and P-glycoprotein that play an important role in dabigatran activation and transport have been studied to date.

Genetic polymorphisms of CES1

The *CES1* genes are located on chromosome 16 and contain 14 exons [10]. More than 2000 different polymorphisms are currently known for *CES1* [8], but only three of them have been shown to be related to the pharmacokinetics of dabigatran: rs2244613 (C > A), rs8192935 (T > C), and rs71647871 (G > A) [6-7, 18]. According to G. Pare et al. (2013), the rs2244613 minor allele was associated with a 15% reduction in minimal dabigatran concentration and a 27% reduction in relative bleeding risk, with this polymorphism present in 32.8% of patients with AF from the RE-LY study [6]. The authors also found that the minor allele of the rs8192935 polymorphism was associated with a 12% reduction in peak dabigatran concentration [6]. In a study by C. Dimatteo et al. (2016) conducted in 92 patients with AF, it was found that the T allele rs8192935 was associated with a reduction in dabigatran concentration compared with carriers of the CC-genotype, with heterozygotes showing a 3% reduction in the residual equilibrium concentration of this drug and homozygotes showing an 11% reduction [7]. However, in heterozygotes and homozygotes for the rs2244613 polymorphism, the residual equilibrium concentration of dabigatran was reduced by only 2% and 3%, respectively [7]. According to D.A.Sychev et al. (2018), no significant effect of the rs2244613 genetic polymorphism on the minimal dabigatran concentration was found in 60 patients undergoing knee replacement, with the minor allele occurring in 27.5% of cases [18]. Another study by this author in patients with AF and stage 3 chronic kidney disease found that the CC-genotype of the rs2244613 polymorphism was associated with a 70% reduction in the dabigatran concentration/dose ratio compared with patients with the AA-genotype [19]. The authors emphasized that in the above patient cohort, investigation of the rs2244613 polymorphism could help improve the safety of dabigatran [19].

In a landmark study by J. Shi et al. (2016), dabigatran etexilate activation was found to be dependent on the rs71647871 polymorphism, which leads to disruption of *CES1* function, associated with a reduction in the conversion of this prodrug and its metabolites to active dabigatran [8], but to our knowledge, no studies have been conducted to evaluate the impact of this polymorphism on dabigatran concentration in clinical practice. In a prospective study by Qiuyi Ji et al. (2021) involving 198 patients with AF taking dabigatran, the minor C allele of the *CES1* rs8192935 polymorphism was associated with an increase in the minimal plasma concentration of this drug [20]. The association described above was also found in patients with the minor A allele of the *CES1* rs2244613

polymorphism (increased minimal plasma concentrations of dabigatran). At the same time, these patients had an increased risk of minor bleeding [20]. A study by Y. Liu et al. (2021) performed in 106 patients showed that the *CES1* rs2244613 polymorphism had no effect on the peak concentration of dabigatran. In contrast, the *CES1* rs8192935 polymorphism was associated with an increase in the peak concentration of this drug [21].

Genetic polymorphisms of P-glycoprotein

The P-glycoprotein is encoded by the gene *ABCB1* (another name for MDR1), which is located on chromosome 7 and contains 29 exons [10]. Currently, more than 1200 polymorphisms of this gene are known, of which the most studied are rs1128503 (1236 C > T), rs2032582 (2677 G > T), rs1045642 (3435 C > T), and rs4148738 (G > A). Different haplotypes are formed from different combinations of the rs1128503, rs2032582, and rs1045642 polymorphisms: *ABCB1*1*, *ABCB1*2*, *ABCB1*13* [22, 23]. The above polymorphisms affect the pharmacokinetics of many drugs that are substrates for P-glycoprotein [10]. At the same time, only the rs1045642 and rs4148738 polymorphisms have been studied for their association with an increase in peak dabigatran concentration [6, 18]. In a study by G.Pare et al. (2013), the presence of the rs4148738 polymorphism was associated with a 12% increase in peak dabigatran concentration, but not with bleeding or ischemic events [6]. At the same time, this position was not confirmed in the work of C.Dimatteo (2016), D.A.Sychev et al. (2018), in which the rs4148738 polymorphism was not associated with significant changes in peak and minimum concentrations of dabigatran [7, 18]. In a study by Q.Xie et al. (2018), the rs4148738 polymorphism also had no significant effect on the pharmacokinetics of dabigatran [24].

The results regarding the rs1045642 polymorphism were generally more encouraging. For example, in Q.Xie et al. (2018) CC carriers of the rs1045642 genotype had lower plasma concentrations of direct oral anticoagulants compared with patients with the TT-genotype [24]. These findings are supported by a study by Sychev et al. which showed that patients with the TT-genotype rs1045642 had higher peak dabigatran concentrations and thus a higher risk of bleeding after knee replacement [18]. A 2021 study by J.Lähteenmäki et al. examined the *ABCB1* rs1045642, rs2032582, rs4148738, and rs1128503 polymorphisms in 1806 patients taking dabigatran, rivaroxaban, and apixaban. In the 340 patients taking dabigatran, in contrast to rivaroxaban and apixaban, no significant effect of the above polymorphisms on the development of thromboembolism and bleeding was detected [25]. These results were also confirmed by Qiuyi Ji et al. (2021), who showed no significant influence of the *ABCB1* polymorphisms rs4148738 and rs1045642 on the pharmacokinetics and pharmacodynamics of dabigatran in patients with AF [20], and by Y.Liu et al (2021), who found no association between the *ABCB1* polymorphisms rs2032582, rs4148738, rs1045642 and the pharmacokinetics of dabigatran in healthy volunteers [21]. At the same time, when the *ABCB1* haplotypes rs2032582 and rs1045642 were combined, the peak concentration of dabigatran was found to increase by 13% and 33% in patients with heterozygous and homozygous mutations,

respectively [26]. Concomitant administration of clarithromycin resulted in a significant increase in dabigatran concentration [26].

An interesting clinical case of left atrial appendage thrombosis was described in the literature, in which dabigatran was taken twice daily at a dose of 110 mg. The patient was heterozygous for the *ABCB1* polymorphisms rs4148738, rs2235046, rs1128503, rs10276036, rs1202169, rs1202168, rs1202167 and homozygous for the *CES1* polymorphisms rs2244613, rs4122238 and heterozygous for the *CES1* polymorphisms rs8192935 and rs4580160. The authors suggested that the above polymorphisms, together with interactions with atorvastatin, which was also taken in this patient, age (70 years), and impaired renal function (creatinine clearance 55 ml/min), may have caused the inefficacy of dabigatran in this case [27]. At the same time, according to the literature, concomitant administration of dabigatran and atorvastatin does not lead to clinically significant interactions and is not associated with changes in the pharmacokinetics and pharmacodynamics of these drugs [28, 29]. In 2020, another case of left atrial ear thrombosis while taking 110 mg of dabigatran for 6 months was published [30]. The patient was found to have three heterozygous *ABCB1* polymorphisms rs4148738, rs1045642, rs2032582 and 2 heterozygous *CES1* polymorphisms rs2244613, rs4580160. The authors suggested that the presence of the above polymorphisms in combination with the administration of amiodarone, which is known to increase plasma concentrations of dabigatran by 12-60% [31], may have influenced the formation of thrombi in the left atrial appendage [30]. In this patient, dabigatran was discontinued, and warfarin was administered, causing the thrombus in the left atrial appendage to resolve after 50 days on this drug [30].

Genetic polymorphisms of uridine-5-diphosphate (UDP) glucuronyltransferase

As mentioned above, metabolism of dabigatran involves conjugation with glucuronic acid to form glucuronides, a process catalyzed by UDF-glucuronyltransferases, among others. It is therefore likely that various genetic polymorphisms of this enzyme may influence the effect of dabigatran. At least three UDF-glucuronyltransferases are involved in the conjugation of dabigatran: *UGT1A9*, *UGT2B7* и *UGT2B15* [10]. According to the in vitro literature, *UGT2B15* contributes the most to the binding of dabigatran to glucuronic acid compared to the other two enzymes [32]. Consequently, it can be assumed that drugs metabolized by the above enzyme (lorazepam, oxazepam, morphine, loratadine, and others) can slow the metabolism of dabigatran when administered concomitantly [33, 34]. At the same time, studies on the effect of the genetic polymorphisms *UGT1A9*, *UGT2B7*, and *UGT2B15* on the pharmacokinetics of dabigatran have not been performed to our knowledge [33]. However, it can be assumed that in patients with the rs1902023 (*UGT2B15*2*) polymorphism of the *UGT2B15* gene, glucuronidation of xenobiotics, including dabigatran, is delayed, which is associated with an increase in the plasma concentration of dabigatran and increases the risk of side effects [35]. This assumption is based on the results obtained for the above polymor-

phism for other drugs that are substrates of UGT2B15, such as oxazepam, acetaminophen, cypoglitazar, etc. [35-38].

Finally, we present information from the PharmGKB pharmacogenomics database [39], according to which the determination of rs2244613 and rs8192935 *CES1* polymorphisms and rs1045642, rs2032582 and rs4148738 *ABCB1* polymorphisms in patients, taking dabigatran has a level of evidence of 3 (low), which does not allow us to recommend the determination of the *CES1* and *ABCB1* data genetic polymorphisms in routine clinical practice because of insufficient or conflicting data. For the other *CES1* and *ABCB1* polymorphisms discussed in this article, no information is available in the PharmGKB database for patients taking dabigatran.

Recently, data from P. Zubiaur et al. (2020) in a study of 107 patients reported that CYP2D6 and CYP3A5 polymorphisms affect the pharmacokinetics and safety of dabigatran [40], which is also reflected in the PharmGKB database with an evidence level 3 [39]. It is also interesting to note that for the most studied *CES1* and *ABCB1* polymorphisms, the authors were unable to demonstrate any association with the pharmacokinetics of dabigatran [40]. However, interpretation of the results should consider that the patients in this study were taking pantoprazole, which is known to be metabolized by the cytochrome P450 system and is thought to affect the pharmacokinetics of dabigatran. Dabigatran, on the other hand, is not metabolized through the cytochrome P450 system, as mentioned above, so the impact of genetic polymorphisms of this system on the pharmacokinetics of dabigatran is questionable and needs to be clarified in further studies.

It should be noted that a literature review by A.V.Savinova et al. was published in 2021 in the journal Rational Pharmacotherapy in Cardiology, also addressing the pharmacogenetics of dabigatran [33]. Although the article is similar in some important respects, our review contains the following differences: it includes an analysis of 2021 literature sources, an analysis of the PharmGKB pharmacogenomics database; our review includes a discussion of a study on the effect of CYP2D6 and CYP3A5 polymorphisms on the pharmacogenetics and safety of dabigatran therapy. If further studies are conducted in this direction, this could be a new aspect of the pharmacogenetics of this drug.

Of course, pharmacogenetics is a relatively new and under-researched field that plays an important role in the development of personalized medicine. The rapid pace of development, accompanied by increasing publication activity, necessitates regular updating of existing knowledge in this field and has been the impetus for the preparation and writing of this review.

CONCLUSION

Currently, there is no conclusive evidence supporting the need for routine determination of the pharmacogenetics of dabigatran in patients with indications for its use in clinical practice. On the other hand, the literature is sparse and often contradictory, so future research in this area is likely to answer the question more precisely.

REFERENCES

1. Hindric Lin S, Wang Y, Zhang L, et al. Dabigatran must be used carefully: literature review and recommendations for management of adverse events. *Drug Des Devel Ther.* 2019;13: 1527-1533. https://doi.org/10.2147/DDDT.S203112.

2. Ahmed S, Levin V, Malacoff R, et al. Dabigatran: a new chapter in anticoagulation. *Cardiovasc Hematol Agents Med Chem.* 2012;10(2): 116-23. https://doi.org/10.2174/187152512800388911.

3. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ.* 2017;28;359: j5058. https://doi.org/10.1136/bmj.j5058.

4. Kryukov AV, Sychev DA, Tereshchenko OV. Pharmacogenetic aspects of new oral anticoagulants application. *Rational Pharmacotherapy in Cardiology.* 2017;13(3): 416-421. (In Russ.). http://doi.org/10.20996/1819-6446-2017-13-3-416-421.

5. Baranova EI, Kobalava ZhD. Dabigatran etexilate in patients with nonvalvular atrial fibrillation: benefits of application in certain clinical situations. *Russian Journal of Cardiology.* 2019;(11): 133-141. (In Russ.). https://doi.org/10.15829/1560-4071-2019-11-133-141.

6. Paré G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation.* 2013;127(13): 1404-12. https://doi.org/10.1161/CIRCULATIONAHA.112.001233.

7. Dimatteo C, D'Andrea G, Vecchione G, et al. Pharmacogenetics of dabigatran etexilate interindividual variability. *Thromb Res.* 2016;144: 1-5. https://doi.org/10.1016/j.thromres.2016.05.025.

8. Shi J, Wang X, Nguyen JH, et al. Dabigatran etexilate activation is affected by the *CES1* genetic polymorphism G143E (rs71647871) and gender. *Biochem. Pharmacol.* 2016;119: 76-84. https://doi.org/10.1016/j.bcp.2016.09.003.

9. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. *Thromb. Haemost.* 2010;103: 572-585. https://doi.org/10.1160/TH09-09-0659.

10. Raymond J, Imbert L, Cousin T, et al. Pharmacogenetics of Direct Oral Anticoagulants: A Systematic Review. *J Pers Med.* 2021;11: 37. https://doi.org/10.3390/jpm11010037.

11. Chang SH, Chou IJ, Yeh YH, et al. Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation. *JAMA.* 2017;318(13): 1250-1259. https://doi.org/10.1001/jama.2017.13883.

12. Bernier M, Lancrerot SL, Rocher F, et al. Major bleeding events in octagenarians associated with drug interactions between dabigatran and P-gp inhibitors. *J. Geriatr. Cardiol.* 2019;16: 806-811. https://doi.org/10.11909/j.issn.1671-5411.2019.11.002.

13. European Medicines Agency. Variation assessment report for Multaq, 2012. Accessed 2021-11-13. Available from https://www.ema.europa.eu/documents/variation-report/multaq-h-c-1043-ii-20-epar-assessment-report-variation_en.pdf

14. Ganetsky M, Babu KM, Salhanick SD, et al. Dabigatran: Review of pharmacology and management of bleeding complications of this novel oral anticoagulant. *J Med Toxicol.* 2011;7: 281-287. https://doi.org/10.1007/s13181-011-0178-y.

15. Ishiguro N, Kishimoto W, Volz A, et al. Impact of endogenous esterase activity on in vitro p-glycoprotein profiling of dabigatran etexilate in Caco-2 monolayers. *Drug Metab. Dispos.* 2014;42: 250-256. https://doi.org/10.1124/dmd.113.053561.

16. Blech S, Ebner T, Ludwig-Schwellinger E, et al. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab. Dispos.* 2008;36: 386-399. https://doi.org/10.1124/dmd.107.019083.

17. Härtter S, Koenen-Bergmann M, Sharma A, et al. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. *Br J Clin Pharmacol.* 2012;74(3): 490-500. https://doi.org/10.1111/j.1365-2125.2012.04218.x.

18. Sychev DA, Levanov AN, Shelekhova TV, et al. The impact of *ABCB1* (rs1045642 and rs4148738) and *CES1* (rs2244613) gene polymorphisms on dabigatran equilibrium peak concentration in patients after total knee arthroplasty. *Pharmgenomics Pers. Med.* 2018;11: 127-137. https://doi.org/10.2147/PGPM.S169277.

19. Sychev D, Skripka A, Ryzhikova K, et al. Effect of *CES1* and *ABCB1* genotypes on the pharmacokinetics and clinical outcomes of dabigatran etexilate in patients with atrial fibrillation and chronic kidney disease. *Drug Metab Pers Ther.* 2020;35(1).

20. Ji Q, Zhang C, Xu Q, et al. The impact of *ABCB1* and *CES1* polymorphisms on dabigatran pharmacokinetics and pharmacodynamics in patients with atrial fibrillation. *Br J Clin Pharmacol.* 2021;87(5): 2247-2255. https://doi.org/10.1111/bcp.14646.

21. Liu Y, Yang C, Qi W, et al. The Impact of *ABCB1* and *CES1* Polymorphisms on Dabigatran Pharmacokinetics in Healthy Chinese Subjects. *Pharmgenomics Pers Med.* 2021;23;14: 477-485. https://doi.org/10.2147/PGPM.S291723.

22. Kim RB, Leake BF, Choo EF, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. *Clin Pharmacol Ther.* 2001;70: 189-199. https://doi.org/10.1067/mcp.2001.117412.

23. Kroetz DL, Pauli-Magnus C, Hodges LM, et al. Sequence diversity and haplotype structure in the human *ABCB1* (MDR1, multidrug resistance transporter) gene. *Pharmacogenetics.* 2003;13: 481-494. https://doi.org/10.1097/00008571-200308000-00006

24. Xie Q, Xiang Q, Mu G, et al. Effect of *ABCB1* Genotypes on the Pharmacokinetics and Clinical Outcomes of New Oral Anticoagulants: A Systematic Review and Meta-analysis. *Curr Pharm Des.* 2018;24: 3558-3565. https://doi.org/10.2174/1381612824666181018153641.

25. Lahteenmaki J, Vuorinen AL, Pajula J, et al. Pharmacogenetics of Bleeding and Thromboembolic Events in

Direct Oral Anticoagulant Users. *Clin Pharmacol Ther.* 2021;110(3): 768-776. https://doi.org/10.1002/cpt.2316.

26. Gouin-Thibault I, Delavenne X, Blanchard A. et al. Interindividual variability in dabigatran and rivaroxaban exposure: contribution of *ABCB1* genetic polymorphisms and interaction with clarithromycin. *J Thromb Haemost.* 2017 Feb;15(2): 273-283. https://doi.org/10.1111/jth.13577.

27. Gu ZC, Ma XW, Zheng XY, et al. Left Atrial Appendage Thrombus Formation in a Patient on Dabigatran Therapy Associated With *ABCB1* and CES-1 Genetic Defect. *Front Pharmacol.* 2018;15;9: 491. https://doi.org/10.3389/fphar.2018.00491

28. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet.* 2008;47(5): 285-95. https://doi.org/10.2165/00003088-200847050-00001.

29. Stangier J, Rathgen K, Stähle H, et al. Coadministration of dabigatran etexilate and atorvastatin: assessment of potential impact on pharmacokinetics and pharmacodynamics. *Am J Cardiovasc Drugs*. 2009;9(1): 59-68. https://doi.org/10.1007/BF03256595.

30. Wu T, Xia X, Fu J, et al. Left atrial appendage thrombus formation in a patient with atrial fibrillation on dabigatran therapy associated with *CES1* and *ABCB1* genetic polymorphisms: A case report. *Medicine (Baltimore)*. 2020;4;99(36): e22084. https://doi.org/10.1097/MD.0000000000022084.

31. Steffel J, Verhamme P, Potpara TS, et al. ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;21;39(16): 1330-1393. https://doi.org/10.1093/eurheartj/ehy136.

32. Ebner T, Wagner K, Wienen W. Dabigatran acylglucuronide, the major human metabolite of dabigatran: in vitro formation, stability, and pharmacological activity. *Drug Metab Dispos.* 2010;38(9): 1567-75. https://doi.org/10.1124/dmd.110.033696.

33. Savinova AV, Dobrodeeva VS, Petrova MM, et al. Pharmacokinetics and Pharmacogenetics of Dabigatran. *Rational Pharmacotherapy in Cardiology* 2021;17(1): 146-152 (In Russ.). https://doi.org/10.20996/1819-6446-2021-01-04.

34. UniProt. UDP-glucuronosyltransferase 2B15. UniProt Knowledgebase Accessed 2021-11-13. Available from: www.uniprot.org/uniprot/P54855.

35. Shnayder NA, Petrova MM, Shesternya PA, et al. Using Pharmacogenetics of Direct Oral Anticoagulants to Predict Changes in Their Pharmacokinetics and the Risk of Adverse Drug Reactions. *Biomedicines.* 2021;22;9(5): 451. https://doi.org/10.3390/biomedicines9050451.

36. He X, Hesse LM, Hazarika S, et al. Evidence for oxazepam as aninvivoprobe of *UGT2B15*: Oxazepam clearance is reduced by *UGT2B15D85Y* polymorphism but unaffected by *UGT2B17* deletion. *Br J Clin Pharmacol.* 2009;68: 721-730. https://doi.org/10.1111/j.1365-2125.2009.03519.x.

37. Court MH, Zhu Z, Masse G, et al. Race, Gender, and Genetic Polymorphism Contribute to Variability in Acetaminophen Pharmacokinetics, Metabolism, and Protein-Adduct Concentrations in Healthy African-American and European-American Volunteers. *J Pharmacol Exp Ther.* 2017;362: 431-440. https://doi.org/10.1124/jpet.117.242107.

38. Stringer F, Ploeger BA, De Jongh J, et al. Evaluation of the Impact of UGT Polymorphism on the Pharmacokinetics and Pharmacodynamics of the Novel PPAR Agonist Sipoglitazar. *J Clin Pharmacol.* 2013;53: 256-263. https://doi.org/10.1177/0091270012447121.

39. Whirl-Carrillo M, Huddart R, Gong L, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clinical Pharmacology & Therapeutics.* 2021; online ahead of print. https://doi.org/10.1002/cpt.2350.

40. Zubiaur P, Saiz-Rodríguez M, Ochoa D. et al. Effect of Sex, Use of Pantoprazole and Polymorphisms in SLC22A1, *ABCB1*, *CES1*, CYP3A5 and CYP2D6 on the Pharmacokinetics and Safety of Dabigatran. *Adv Ther.* 2020;37(8): 3537-3550. https://doi.org/10.1007/s12325-020-01414-x.