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Pharmacogenetics of Direct Oral Anticoagulants

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Abstract

For more than 50 years, oral vitamin K antagonists were the choice of anticoagulant for the long-term treatment and prevention of arterial and venous thromboembolic events. In recent years, four direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban and edoxaban have been compared with warfarin for thromboembolism prevention. These anticoagulants directly inhibit specific proteins within the coagulation cascade; in contrast, oral vitamin K antagonists inhibit the synthesis of vitamin K-dependent clotting factors. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, the factor Xa inhibitors, produce a more predictable, less labile anticoagulant effect. DOACs do not have limitations inherent vitamin K antagonists. DOACs have a predictable pharmacokinetic profile and are free of adverse drug reactions inherent in vitamin K antagonists. However, it is necessary to take into account the pharmacogenetic characteristics of the individual that can affect effectiveness and safety of use of DOACs. The results carried out to the present fundamental and clinical studies of DOACs studies demonstrate an undeniable influence of genome changes on the pharmacokinetics and pharmacodynamics of DOACs. However, the studies need to be continued. There is a need to plan and conduct larger studies in various ethnic groups with the inclusion of sufficient associative genetic studies of the number of patients in each of the documented groups treatments with well-defined phenotypes.

Keywords: dabigatran etexilate, dabigatran, rivaroxaban, apixaban, edoxaban, pharmacogenetics, effectiveness, safety, single nucleotide variant, CES1, ABCB1, ABCG2, CYP3A5, CYP2C9, CYP2J2, SLCO1B1, UGT1A9, UGT2B7, UGT2B15

1. Introduction

Thromboembolism (such as stroke and systemic embolism) is a serious complication of non-valvular atrial fibrillation (AF) [1]. Pulmonary embolism (PE) can cause death within first 14 days after a stroke in 25–50% of cases [2]. In absence of preventive measures, venous thromboembolic complications in lower limb arthroplasty (deep vein thrombosis and PE) reached 15–30% of cases before widespread use of anticoagulant therapy in clinical practice. However, with introduction of new anticoagulants in 2001, these indicators decreased to 1–2% [3], and in recent years to 0.7–1.7% of [4]. Long-term use of anticoagulants is necessary for prevention of

thromboembolic complications in patients with high risk of thromboembolism. For long time, vitamin K antagonists (warfarin, acenocumarol, phenindione) and indirect thrombin inhibitors (heparins) were used as drugs to prevent occurrence of thromboembolic complications [5, 6]. However, despite its effectiveness, coumarin therapy has some limitations. Drugs of this group are characterized by delayed therapeutic effect (after 36–72 hours from start of administration, with development of maximum effect on 5–7 days from start of use) [7]. Also, there is a need for regular therapeutic drug monitoring with the control of international normalized ratio (INR) indicator at safe level within 2–3, which entails additional economic burdens on health system [8]. A significant disadvantage of this group of drugs is irreversibility of drug in the event of an overdose [9]. The deviation of the INR from the permissible limits, both in lower and in higher direction, is prognostically unfavorable indicator. In first case, the therapeutic effect of anticoagulant therapy will not be achieved. In second case, the risk of hemorrhagic complications increases [10]. Balancing the effectiveness and safety of anticoagulant therapy is a difficult task in real clinical practice. Genetically determined features of individual's enzyme systems involved in drug metabolism make significant contribution to their effectiveness and safety [11]. An alternative to vitamin K antagonists were direct oral anticoagulants (DOACs), which do not have limitations inherent in warfarin [12]: dabigatran, rivaroxaban, apixaban, endoxaban. DOACs have a predictable pharmacokinetic profile and are free of disadvantages inherent in vitamin K antagonists. However, it is necessary to take into account the pharmacogenetic characteristics of the individual that can affect effectiveness and safety of use of DOACs.

2. Dabigatran

Dabigatran etexilate is first DOAC that has direct reversible inhibitory effect on thrombin [13, 14]. Thrombin is catalyst for conversion of factors V, VIII and XI in blood clotting cascade, and also catalyzes conversion of fibrinogen to fibrin and factor XIII to factor XIIIa, which contributes to stabilization of fibrin [15]. Also, thrombin activates GPCR receptors, which leads to conformational changes in platelets and promotes their aggregation. This leads to the release of even more clotting factors and the formation of more thrombin [16].

After entering the human body, dabigatran etexilate, being an inactive precursor (prodrug), quickly turns into an active metabolite – dabigatran. Dabigatran reversibly binds to the active center of the thrombin molecule, preventing thrombin-mediated activation of clotting factors. An important feature of dabigatran is that it can inactivate thrombin, even if it is in a bound state with fibrin [17]. The maximum concentration (C_{max}) of dabigatran in plasma and, accordingly, anticoagulant action is observed as early as 0.5–2 hours after oral administration [18]. The half-life ($T_{1/2}$) of dabigatran with a single dose is 11 hours, but with regular intake it increases to 12–14 hours, which allows you to prescribe dabigatran etexilate 2 times a day [19]. Approximately one-third of the dabigatran circulating in blood binds to proteins. The drug is excreted unchanged from the body: 85% - with kidneys, 15% - with bile [20, 21].

It is important that dabigatran etexilate is not metabolized by cytochrome P450 isoenzymes of liver and does not change their activity. The CES1 and CES2 enzymes are human liver carboxylesterases that hydrolyze various xenobiotics and endogenous substrates using ester or amide bonds. Conversion of dabigatran etexylate to dabigatran depends more on activity of CES1 than on activity of CES2 [22–24].

Glycoprotein P (P-gp) is an ATP-dependent transporter that is involved in transfer of substrate molecules across membranes of expressing cells and components

(regardless of concentration gradient) [25, 26]. P-gp is widely present in human body tissues and plays leading role in pharmacokinetics of dabigatran etexilate, which is a substrate for P-gp [13]. It is necessary to take into account drug interaction when prescribing dabigatran etexilate with P-gp inhibitors (verapamil, amiodarone, carvedilol, quinidine, spironolactone, nicardipine, propafenone, atorvastatin, clarithromycin, erythromycin, fluoroquinolones, ketoconazole, itraconazole, cyclosporine, fluoxetine, paroxetine, pentazocine, ritonavir, lopinavir, grapefruit juice, and others), as this leads to decrease in its effectiveness, increased absorption of these drugs, inhibition of their excretion, and increased penetration through barriers. This leads to an increase in the concentration of P-gp substrate drugs in the blood and tissues and increases the risk of adverse drug reactions (ADRs). Bernier et al. revealed development of bleeding in 30.4% of patients taking P-gp inhibitors together with dabigatran [27]. On contrary, drugs that are inducers of P-gp (rifampicin, morphine, dexamethasone, retinoids, barbiturates, nicotine, diphenin, isoniazid, carbamazepine, caffeine, diazepam, diphenhydramine, tricyclic antidepressants, phenytoin, ethanol), when used with dabigatran, by increasing activity of P-gp, lead to inhibition of dabigatran absorption, increase its elimination and inhibition of penetration through barriers. This leads to decrease in concentration of P-gp substrate drug and a decrease in its effectiveness. It is also important to take into account that simultaneous use of substrates and P-gp inhibitors increases the risk of developing congenital anomalies in fetus [28].

In addition to *CES1* and *ABCB1*, which affect biotransformation of dabigatran etexilate and the effectiveness of active dabigatran, glucuronidation enzymes *UGT2B15*, *UGT1A9*, and *UGT2B7* also participate in its metabolism (elimination). Their activity reflects safety of using dabigatran [29]. The main and most interesting enzyme involved in elimination of dabigatran is *UGT2B15*. When prescribing dabigatran etexilate, it is important to consider drug interactions with drugs that are metabolized by *UGT2B15*. By interacting competitively with enzyme, they can slow down metabolism of dabigatran (for example, acetaminophen, loratadine, lorazepam, oxazepam, morphine, valproic acid) [30, 31], and its concentration will increase, increasing the risk of ADRs.

To date, the *CES1* and *ABCB1* genes have been shown to have an important effect on metabolism of dabigatran etexilate, and single-nucleotide variants (ONVs) in these two loci probably play key role. There are many studies conducted worldwide to find out whether search for ONVs in *CES1* and *ABCB1* genes can explain some of inter-individual variability in the concentrations of the active metabolite dabigatran in the blood of humans, and *UGT2B15* gene may be potential candidate gene for safety studies of dabigatran. Paré et al. investigated the ONV of *CES1* gene to assess inter-individual profile of efficacy and safety of dabigatran as part of RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy study) [32]. Carriage of minor allele G (rs2244613) of *CES1* gene occurred in 32.8% of patients and was associated with minimal concentrations of dabigatran in the blood and, consequently, with a lower risk of bleeding ($p < 9 \times 10^{-8}$) [32]. Dimatteo et al. [33] found association of rs8192935 of *CES1* gene with a lower concentration of dabigatran in blood plasma ($p = 0.023$). Carriers of allele T showed significantly lower concentrations of dabigatran in blood plasma than carriers of homozygous CC genotype, which reduces the risk of hemorrhagic complications. Overall, the average plasma concentration of dabigatran was higher in patients with the CC genotype (86.3 ng/DL) than in patients with the allele T (62.1 ng/DL). At the same time, there was no significant effect of rs4148738 of *ABCB1* gene on concentration of dabigatran in blood [33].

Gouin-Thibault et al. [26] evaluated effect of clarithromycin on pharmacokinetics of dabigatran in 60 healthy male volunteers selected for *ABCB1* genotype (20

homozygous carriers of ONVs, 20 heterozygous and 20 homozygous carriers of the wild-type allele for haplotype 2677–3435). The results of the study AUC (Area Under the Curve – area under the curve) was 77% for dabigatran. The *ABCB1* genotype did not significantly affect pharmacokinetics of dabigatran: AUC ratio in carriers of studied ONVs and wild-type allele carriers was 1.27 (95% confidence interval (CI) 0.84–1.92), but clarithromycin administration led to twofold increase in AUC for dabigatran, regardless of *ABCB1* genotype: and was 2.0 (95% CI 1.15–3.60) [29].

The aim of the study is Shi et al. [24] studied effect of the ONVs of *CES1* gene and gender of patients on effectiveness of dabigatran using several in vitro approaches. Thus, 104 biopsy samples obtained from liver of patients of various racial backgrounds were examined for carriers of three ONVs: rs2244613, rs8192935, and rs71647871 or G428A, also referred to as G143E, which is variant of *CES1* with reduced enzymatic activity. The study showed that G143E is ONV with reduced metabolism for dabigatran. The activity of *CES1* enzyme was significantly higher in female liver samples than in male liver samples. The data obtained by the authors indicate that the studied ONVs of *CES1* and the gender of patients are important risk factors contributing to variability of the pharmacokinetics of dabigatran etexilate in humans. A personalized approach to treatment with dabigatran etexilate should be based on identifying patient-specific genetic changes in the *CES1*. This approach can potentially improve the effectiveness and safety of pharmacotherapy with this drug [24].

The activity of glucuronidation enzymes depends on the ONVs of their encoding genes. To date, we have not found any works that would present studies of association of carrier of the *UGT* family genes on metabolism of dabigatran in humans. However, we can assume that this may change its concentration in blood plasma of patients. This hypothesis is based on previous studies of associations of ONVs carrier of *UGT2B15* gene on concentration of drugs that are metabolized in a similar way to dabigatran. He et al. [34] found that carriage of allele A (rs1902023) of the *UGT2B15* gene is associated with decrease in oxazepam clearance. In other words, in patients with this allele, glucuronidation of xenobiotics is slower, and concentration of drugs in blood plasma increases, thereby increasing the risk of developing ADRs [34]. A similar change in glucuronidation of drugs in carriers of this ONVs is shown for other drugs that are metabolized in similar way (lorazepam [31], acetaminophen [35], tamoxifen [36], valproic acid [37]). In study of pharmacokinetics of cypoglitazarus Stringer et al. [38] showed that patients homozygous for *UGT2B15**2 (rs1902023 G > T) had significantly higher concentrations of this drug in blood compared to patients carrying *UGT2B15**1 genotypes/*2 or *UGT2B15**1/*1 [38]. Thus, carrier is rs1902023 (*UGT2B15**2) of *UGT2B15* gene is associated with delayed glucuronidation and is important predictor of interindividual variability in drug clearance. Therefore, this effect can have significant effect on metabolism of dabigatran as substrate of *UGT2B15*.

3. Rivaroxaban

Rivaroxaban is the first direct factor Xa inhibitor. Pharmacokinetics of rivaroxaban does not have disadvantages of vitamin K antagonists. However, pharmacokinetics and pharmacogenetics of rivaroxaban are variable. This can affect both effectiveness and safety of anticoagulant therapy.

Rivaroxaban inhibits platelet activation and fibrin clot formation by direct, selective and reversible inhibition of factor Xa in both intrinsic and extrinsic coagulation pathways. Factor Xa, as part of prothrombinase complex, also composed of factor Va, calcium ions, factor II, and phospholipids, catalyzes the conversion of

prothrombin to thrombin. Thrombin activates platelets and catalyzes the conversion of fibrinogen to fibrin. Thus, factor Xa is a coagulation factor that acts at point of convergence of internal and external pathways in blood coagulation system. It catalyzes the breakdown of prothrombin and is therefore critical for thrombin generation. It is important to note that rivaroxaban inhibits free prothrombinase- and clot-associated factor Xa without directly affecting platelet aggregation [39]. This distinguishes rivaroxaban from indirect inhibitors of factor Xa, which does not inhibit factor Xa associated with prothrombinase complex [40].

When taken orally, rivaroxaban reaches its maximum plasma concentration after 2–4 hours. The absolute bioavailability of rivaroxaban for dosage of 10 mg is relatively high (80–100%) and does not depend on food intake [41, 42]. Under fasting conditions, oral bioavailability of rivaroxaban at dosage of 20 mg decreases to 66%. When using drugs at a dosage of 20 mg with food, the AUC increases to 39%. This indicates an almost absolute absorption and, at same time, a high oral bioavailability of rivaroxaban. The connection with plasma proteins reaches 92–95%. Because of this high plasma protein binding, rivaroxaban is not removed during dialysis [43].

Rivaroxaban is eliminated from body in various ways, of which three are main ones. Approximately 36% of dose is excreted unchanged by kidneys through active transporter-mediated secretion by P-glycoprotein (Pgp) and BCRP (ABCG2). In addition, 14% of dose is eliminated by hydrolysis of amide bonds and 32% of dose is eliminated via oxidative metabolic pathways. Liver isoenzymes CYP3A4 and CYP3A5 are responsible for metabolism about 18%, and CYP2J2 - about 14% of the dose [44, 45]. Level of rivaroxaban when administered concomitantly with midazolam (a CYP3A4 substrate) is reduced by an average of 11% compared with rivaroxaban alone. The following drugs moderately alter the level of rivaroxaban: erythromycin (a moderate inhibitor of CYP3A4/P-gp; an increase of 34%); clarithromycin (potent CYP3A4/mild P-gp inhibitor; 54% increase); fluconazole (moderate CYP3A4, a possible inhibitor of BCRP (ABCG2); an increase of 42%). A significant increase in blood levels and strength of action of rivaroxaban has been demonstrated when used simultaneously with drugs that are potent inhibitors of the CYP3A4 enzyme and P-gp/BCRP transporter proteins (ABCG2) and potential inhibitors of CYP2J2 enzyme, for example: use of ketoconazole 400 mg once a day leads to an increase in level of rivaroxaban by 158% (95% CI: 136% - 182%); the use of ritonavir increases level of rivaroxaban by 153% (95% CI: 134% - 174%) [46].

The expression of rivaroxaban transporter proteins may be influenced by SNVs of *ABCB1* gene, but information on their clinical significance is inconsistent. The systematic review and meta-analysis by Xie et al. [47] showed that C_{max} was lower in carriers of *ABCB1* rs1045642 CC than carriers of TT, and carriers of rs2032582 GG than carriers of A/T allele, and $AUC_{0-\infty}$ was lower in rs1045642 CC carriers than in TT carriers [47]. In the study by Gouin-Thibault et al. [26] found that *ABCB1* polymorphisms is not significant determinant of individual variability in pharmacokinetics of rivaroxaban, and combined use of P-gp/CYP3A4 inhibitor clarithromycin with rivaroxaban may require caution in patients at risk of overdose, as it leads to two-fold increase in AUC genotype *ABCB1* [26].

In the study by Sychev et al. found no significant differences in peak steady-state concentration of rivaroxaban between mutant haplotypes and wild haplotypes of *ABCB1* gene [48]. The similar result was posted by Sennesael et al. [49]: ONVs 1236 C > T, -2677 G > T-3435, C > T and 1199 G > A of *ABCB1* gene did not significantly affect the intracellular accumulation of rivaroxaban compared to wild-type protein. These results suggest that *ABCB1* SNVs studied in present study are unlikely to contribute to individual variability in plasma rivaroxaban concentrations [49]. At same time, it was found that use of strong inhibitors and inducers of P-gp should be avoided in patients taking rivaroxaban [26, 50].

Promising direction is study of BCRP protein, encoded by *ABCG2* gene, which, like P-gp, provides absorption and excretion of rivaroxaban from intestinal lumen and renal tubules. The *ABCG2* gene is increasingly recognized as an important mediator of drug transport in the intestine and renal tubules [51], and its SNVs affect decrease in BCRP substrate transport in case of co-administration of rivaroxaban and other drugs [52]. Most studied SNVs in this gene, Q141K (rs2231142), is associated with decrease in *ABCG2* activity and, consequently, with a decrease in activity of its drug substrates transport [53]. This SNVs has not yet been studied in context of pharmacogenetics of rivaroxaban; however, in an experimental mouse model, absence of P-gp (*ABCB1*) and BCRP (*ABCG2*) was associated with significantly reduced drug clearance [54].

Metabolism of rivaroxaban in liver is carried out by cytochrome P450 isoenzymes 3A4 (*CYP3A4*) and 2J2 (*CYP2J2*), as well as by mechanisms independent of CYP [46]. To date, more than 50 SNVs of *CYP3A4* gene have been discovered, associated with different levels of activity of *CYP3A4* isoenzyme. Associations between *CYP3A4* SNVs carriage and changes in pharmacological response have been described for atorvastatin, simvastatin, sacrolimus, and fentanyl [55]. Information on the change in pharmacological response of rivaroxaban in literature available to us was not found. At same time, it was found that use of strong inhibitors and inducers of *CYP3A4* and P-gp should be avoided in patients taking rivaroxaban [50]. For example, “old” antiepileptic drugs (AEDs) that act on cytochrome P450 isozymes, and especially on *CYP3A4*, such as phenobarbital, phenytoin, and carbamazepine, are more likely to significantly reduce the anticoagulant effect of DOACs (especially rivaroxaban, apixaban, and edoxaban). New AEDs that do not significantly affect CYP or P-gp, such as lamotrigine or pregabalin, are unlikely to affect the effectiveness of DOACs. Zonisamide and lacosamide, which do not significantly interfere with in vitro CYP activity, may have a safe profile. However, their effect on P-gp has not yet been studied. Levetiracetam only has a potential effect on P-gp activity, so it may also be safe [56].

The study of effect of a potent P-gp inhibitor cyclosporin and its combination with a moderate *CYP3A* inhibitor fluconazole on pharmacokinetics of rivaroxaban and *CYP3A* activity (compared with baseline) showed that cyclosporine increased average exposure of rivaroxaban by 47%, maximum concentration of *CYP3A4* and decreased by 34%, and cyclosporine in combination with fluconazole increased the average exposure of rivaroxaban by 86% and maximum concentration by 115%. This effect was significantly stronger than that observed in control group that received rivaroxaban with fluconazole alone [57].

The high clinical significance of interaction of rivaroxaban with other drugs is shown in a systematic review and meta-analysis of studies in which patients with atrial fibrillation were randomized to groups taking DOACs or warfarin, stratified by number of concomitant drugs [58]. Polypharmacy was significantly associated with poor outcomes and reduced the benefit in terms of risk of major bleeding in patients receiving rivaroxaban, especially in presence of drugs that modulate P-gp/*CYP3A4*.

Also, about 10 different SNVs for *CYP2J* gene are known, but their clinical role was mainly studied in the context of coronary heart disease (CAD) and arterial hypertension, since isoenzyme *CYP2J* encoded by this gene plays a role in the metabolism of arachidonic acid [59].

4. Apixaban

Apixaban is a potent direct oral reversible and highly selective factor Xa inhibitor that does not require antithrombin III for antithrombotic activity [60, 61]. Apixaban

inhibits both free and clot-associated factor Xa and prothrombinase activity, which inhibits clot growth [62]. By inhibiting factor Xa, apixaban reduces formation of thrombin and development of blood clots. It has no direct effect on platelet aggregation, but indirectly inhibits thrombin-induced platelet aggregation [63].

Absorption of apixaban occurs mainly in small intestine and gradually decreases as it passes through it [64]. For oral doses up to 10 mg, absolute bioavailability of apixaban is about 50% due to incomplete absorption [65, 66] and first passage through liver [67, 68]. Apixaban C_{max} in plasma is reached 3–4 hours after oral administration [69, 70]. Binding of apixaban to blood plasma proteins, mainly albumin, is about 87% [71]. After oral administration, unchanged apixaban is main drug component in human blood plasma without presence of active circulating metabolites [66]. Excretion of apixaban involves several pathways, including metabolism in liver, as well as excretion by unchanged parent compound in bile and kidneys, and direct intestinal excretion [72].

Metabolic pathways of apixaban include O-demethylation, hydroxylation, and sulfation of hydroxylated O-demethylapixaban [66]. At same time, metabolism mainly occurs through isoenzymes CYP3A4 /5 of liver cytochrome P450, with an insignificant participation of isoenzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2J2 [67].

The role of non-functional allele G (rs776746) of *CYP3A5* gene has been most studied. At same time, in heterozygous carriers (genotype AG), metabolism of apixaban is moderately reduced due to carriage of one non-functional allele G, and in heterozygous carriers (*CYP3A5**3, genotype GG) *CYP3A5* isoenzyme is not expressed. This is a risk factor for development of ADRs (in particular, bleeding) when taking apixaban [73]. Ueshima et al. found that patients with AF and a homozygous TT genotype (rs77674) of *CYP3A5* gene may have decreased blood apixaban concentrations compared to patients with CC and CT genotypes. Therefore, carriage of allele T may be associated with an increased clearance of apixaban [73]. However, this study was conducted on patients from Asian population, which does not allow extrapolation of the results to other racial and ethnic groups.

The highest risk of developing apixaban-induced ADRs due to a slowdown in the metabolism of drug in liver, especially when combined with drugs-inhibitors of *CYP3A5* isoenzyme, in homozygous carriers of non-functional alleles *CYP3A5**2 (rs28365083), *CYP3A5**3 (rs776746), *CYP3A5**6 (rs10264272), *CYP3A5**7 (rs41303343), *CYP3A5**8 (rs55817950), *CYP3A5**9 (rs28383479), *CYP3A5**10 или *CYP3A5**3 K (rs41279854), *CYP3A5**11 (rs72552791), *CYP3A5**3D (rs56244447), *CYP3A5**3F (rs28365085), *CYP3A5*_3705C > T(H30Y) (rs28383468), *CYP3A5*_7298C > A(S100Y) (rs41279857). Among them, the most common is non-functional allele *CYP3A5**3 (rs776746). In terms of phenotypes, individuals are “expressors” of *CYP3A5* if they carry at least one *CYP3A5**1 allele, and “non-expressors” if not. It should be noted that frequency of carriage of SNVs of *CYP3A5* gene varies significantly depending on ethnicity of patients. For example, most Europeans are not expressors, while many people of African descent are *CYP3A5* expressors [63, 74]. Higher concentrations of active component of drugs, metabolized with participation of isoenzyme *CYP3A5*, in blood plasma are higher in non-expressors of *CYP3A5* compared with expressors [75]. In patients belonging to group of non-expressing *CYP3A5* (homozygous carriers of the above non-functional alleles), apixaban dosing should be cautious and requires monitoring of ADRs. Co-administration of apixaban with other drugs metabolized with participation of *CYP3A5* isoenzyme should be avoided in non-expressors,

The study SNVs of *CYP3A5* gene was conducted among 200 postmenopausal women who had an episode of venous thromboembolism and more than 500 comparable control groups. It is known that oral estrogen intake increases the

risk of venous thromboembolism in all women (odds ratio (OR) - 4.5; CI: 2.6–7). Compared with women who did not receive oral estrogens, the OR for venous thromboembolism in users of oral estrogens was 3.8 (CI: 2.1–6.7) among women who did not have the common (wild) CYP3A5 * 1 allele encoding a highly functional isoenzyme CYP3A5, and 30.0 (CI: 4.4–202.9) among patients with this allele (interaction test $p = 0.04$) [76]. This is important to consider when prescribing apixaban to postmenopausal women.

Carriage of low-functional alleles CYP1A2*1C (rs2069514), CYP1A2*1K_-729C > T (rs12720461), CYP1A2*1K_-739 T > G (rs2069526), CYP1A2*3 (rs56276452), CYP1A2*4A (rs56276455), CYP1A*4A (rs28399424) of CYP1A2 gene leads to decrease in activity of CYP1A2 isoenzyme. This may be of clinical significance in long-term therapy with apixaban in homozygous carriers of low- or non-functional alleles of CYP3A5 gene, due to the cumulative risk and disruption of auxiliary pathway of apixaban metabolism in the liver with the participation of the isoenzyme CYP1A2. This reduces metabolism of drug and increases the risk of ADRs. In addition, in carriers of CYP1A2*1C (rs2069514), concomitant use of apixaban with inhibitors of the isoenzyme CYP1A2 may slow down the breakdown of caffeine, which can lead to overstimulation by caffeine. On contrary, carriage of highly functional allele CYP1A2*1F (rs762551) can lead to an acceleration of apixaban metabolism. Smoking is a well-known CYP1A2 activator (especially in CYP1A2*1F carriers). This leads to a more rapid degradation of drugs metabolized with the participation of CYP1A2 isoenzyme, and possibility of insufficient concentration of drugs in body to obtain significant therapeutic benefits [77].

Carriers of SNVs of CYP2C9 gene can metabolize drugs in different ways. From a clinical point of view, it is important of carriage of the following SNVs: rs1057910 (two variants that encode the “wild-type” CYP2C9*1 allele and the non-functional CYP2C9*3 allele), as well as rs1799853, rs9332131, rs72558190, rs72558 (non-functional variants CYP2C9*2, CYP2C9*6, CYP2C9*15, CYP2C9*25 respectively). In particular, the carriage of non-functional alleles CYP2C9*2 and CYP2C9*3 should be taken into account when co-administration of apixaban and clopidogrel, which inhibits the CYP2C9 isoenzyme in sufficiently high doses. This may affect the metabolism of drugs that are metabolized with the participation of the isoenzyme CYP2C9, and patients who are homozygous carriers of non-functional alleles of CYP2C9 (slow metabolizers) are likely to be at greater risk of ADRs (in particular, the risk of bleeding) when taking clopidogrel and apixaban [78].

Some of major metabolic pathways of apixaban include o-demethylation, hydroxylation, and sulfation, with o-demethylapixaban sulfate being main metabolite [66]. Potentially important pharmacogenomic metabolic pathway is via sulfotransferases (SULT) SULT1A1 and SULT1A2, which are responsible for sulfation of o-demethyl-apixaban to o-demethyl-apixaban sulfate [79, 80]. SULT1A1 enzyme is more efficient than SULT1A2 in sulfation of o-demethyl-apixaban [81]. O-demethyl-apixaban is the most well-known metabolite and accounts for 25% of the estimated active apixaban [66]. It is important to know that o-demethyl-apixaban sulfate does not have any inhibitory activity against factor Xa, which may contribute to anticoagulant efficacy of apixaban [81]. Three important SNVs of SULT1A1 gene have been described: SULT1A1*1 (wild type), SULT1A1*2 (rs9282861), and SULT1A1*3 (rs1801030) [80]. V_{max} of all three allelic variants of SULT1A1 gene (SULT1A1*1 > SULT1A1*3 > SULT1A1*2) varies, and this explains the differences in sulfation of active apixaban. The SULT1A*3 variant has a moderate potential to influence anticoagulant effect of apixaban, whereas SULT1A*2 has low potential to influence apixaban metabolism [82]. These different alloenzymes have different enzymatic efficiencies and can lead to different concentrations of metabolites and variations in anticoagulant efficacy of apixaban [83]. However, the effect

of common genetic variants of *SULT1A1* gene on apixaban metabolism in patients has not yet been formally studied [78].

5. Edoxaban

Edoxaban is a selective, direct and reversible inhibitor of activated blood coagulation factor X (F Xa), a serine protease responsible for thrombin formation. Edoxaban is used to prevent stroke in nonvalvular AF, treat deep vein thrombosis and PE [84–86].

It binds to both free FXa and free FXa in prothrombinase complex, thus causing a dose-dependent decrease in thrombin formation [87].

Edoxaban is characterized by linear, predictable pharmacokinetic profile [88]. After oral administration, edoxaban reaches peak plasma concentrations (C max) within 1–2 hours [89]. The half-life (T_{1/2}) of edoxaban is approximately 10–14 hours [88]. Edoxaban is absorbed mainly in upper gastrointestinal tract, approximately 13% is absorbed in large intestine [90].

In an in vitro study, five phase 1 metabolites of edoxaban were found in human liver microsomes: M-1, M-4, M-5, M-6 and a hydroxylated metabolite at the N-dimethylcarbamoyl group of edoxaban (hydroxymethylenedoxaban) (M-7) [91]. Formation of a metabolite M-4, unique for humans, is catalyzed by CES1, which is present in human liver microsomes and in the cytosol. Cytochrome P450 (CYP) 3A4 isoenzyme mediates formation of M-5 and hydroxymethylenedoxaban in presence of nicotinamide adenine dinucleotide phosphate (NADPH). It is assumed that M-8, minor metabolite, arises spontaneously (non-enzymatically) via an intermediary, hydroxymethylenedoxaban, which is formed via CYP3A4/5 [92].

Second phase of edoxaban metabolism is mediated by glucuronidation to form N-glucuronide metabolite (M-3). This metabolite has not been quantified. Three metabolites (M-4, M-6 and M-8) have anticoagulant activity with half-maximum inhibitory concentration (IC₅₀) values for anti-FXa 1.8 nM (M-4), 6.9 nM (M-6) and 2.7 nM (M-8). The IC₅₀ value of edoxaban for anti-FXa is 3 nM [93]. However, due to its low content and high protein binding (80%), it is expected that most abundant metabolite M-4 will not make a significant contribution to overall pharmacological activity of edoxaban in patients with at least a moderate decline in renal function [94]. Other metabolites are present in even smaller amounts and (in the absence of liver cytochrome P450 inducers) do not significantly contribute to total anticoagulant activity of drugs. None of metabolic pathways alone contributes more than 10% to total clearance of edoxaban [92].

Edoxaban is a substrate for P-gp and is not a substrate for other transporters such as anion transport polypeptide (OATPs), 1B1, or organic cation transporters (OATs) 2 [95].

Edoxaban is mainly excreted unchanged in urine and through the secretion of biliary tract with feces [92]. Renal clearance of unchanged drugs is approximately 50% of total clearance, and remaining 50% of non-renal clearance occurs due to metabolism and secretion of the biliary tract. As previously described, edoxaban is metabolized by the enzymes CES1 (<10%), CYP3A4 (<10%) and by glucuronidation; but metabolism is a minor route of elimination of edoxaban in patients with normal renal function. Therefore, inhibitors or inducers of these enzymes are unlikely to have clinically significant interactions with edoxaban. However, drug interaction studies have been performed to investigate the effect of CYP3A4 inhibitors on the pharmacokinetics of edoxaban. In addition, the effects of other drugs that could be administered concurrently with edoxaban were evaluated. Since edoxaban is a substrate of the P-gp efflux transporter, several studies have

been carried out on interaction of drugs with inhibitors, substrates and inducers of P-gp. The effect of co-administration of P-gp inhibitors was an increase in effect of edoxaban (maximum observed drug concentration in plasma C_{max} and area under the curve of concentration versus time AUC), but the increase was less than 2 times. P-gp inhibitors and potent CYP3A4 / 5 inhibitors (eg, ketoconazole, erythromycin) do not result in greater increases in exposure compared to mild P-gp inhibitors (eg verapamil) or mild inhibitors (eg cyclosporine) CYP3A4 / 5. This confirms that the metabolism of CYP3A4/5 is not the main route of elimination of edoxaban [96, 97].

Co-administration of ketoconazole (P-gp inhibitor; potent CYP3A4 inhibitor) increased the single dose peak and overall exposure to edoxaban by 89% and 87%, respectively [98]. However, co-administration of oral quinidine (P-gp and OCT2 transporter inhibitor; potent CYP2D6 inhibitor) increased the single dose peak and 24-hour exposure of oral edoxaban by 85% and 77%, respectively [99].

Co-administration of sustained-release verapamil (P-gp inhibitor (main effect); moderate CYP3A4 inhibitor) increased the peak and 24-hour exposure of single doses of edoxaban by 53% [99].

Co-administration of erythromycin (P-gp inhibitor; moderate CYP3A4 inhibitor) increased the peak and total exposure of single doses of edoxaban by 68% and 85%, respectively [91]. Co-administration of cyclosporine (P-gp inhibitor, OATP1B1 and BCRP; weak inhibitor of CYP3A4) increased both the peak and total exposure of single doses of edoxaban by 74% and 73%, respectively [98]. Co-administration of dronedarone (a P-gp inhibitor) increased the peak and total exposure of single doses of edoxaban by 46% and 85%, respectively [99].

The administration of amiodarone (P-gp inhibitor; moderate CYP2C9 inhibitor, weak CYP2D6 inhibitor) to patients receiving edoxaban for 3 days of once daily administration increased the peak and total exposure of single doses of edoxaban by 66% and 40%, respectively [99]. This is important to remember because amiodarone has a long half-life, reaching an average of 58 days [100]. Rifampicin, inducer of P-gp (strong CYP3A4 inducer; moderate inducer of CYP2B6, 2C8, 2C9, 2C19; inhibitor of P-gp, OATP1B1, OATP1B3) after 7 days of dosing reduced the total exposure to edoxaban by about 34%, without affecting its peak exposure [101]. Co-administration of digoxin (P-gp substrate) increased the C_{max} of edoxaban by 16% without significantly affecting overall exposure or renal clearance at steady state [99].

At the same time, atorvastatin (OATP1B1 and OATP1B3 substrate; weak CYP3A4 inhibitor), when taken together with edoxaban, does not affect the peak or total exposure of edoxaban [99]. Co-administration of naproxen and edoxaban also had no effect on the peak and total exposure of edoxaban. However, led to an increase in the duration of bleeding compared with each drug administered separately. Co-administration of naproxen increased the baseline-adjusted bleeding time ratio by 72% on day 2 compared with edoxaban alone (90% CI: 139.3–213.3). In contrast, concomitant administration of edoxaban with naproxen increased the equivalent bleeding time by 22% compared with naproxen alone (90% CI: 98.1–151.0) [102]. Naproxen reduced the baseline-adjusted platelet aggregation coefficient on the 2nd day of co-administration by 69.89% (90% CI: 68.20–71.62), while edoxaban itself did not affect platelet aggregation.

Co-administration of high doses of aspirin (325 mg) increased the stationary peak and total exposure of edoxaban by 34% and 30%, respectively, and decreased renal clearance by 17%, possibly due to inhibition of active renal secretion. Co-administration of low-dose aspirin (100 mg) did not affect the peak or total exposure of edoxaban either after a single dose or with stable use (90% CI: 80–125%). Co-administration of edoxaban and aspirin at low (100 mg) or high (325 mg) doses resulted in an additive effect in terms of increased bleeding time. The anticoagulant effects of edoxaban were not affected by the simultaneous

administration of aspirin. Coadministration of low doses of aspirin (100 mg) did not significantly affect INR, prothrombin time (PTI), activated partial thromboplastin time (APTT), or intrinsic FXa activity [102]. Enoxaparin did not affect the peak and total exposure of edoxaban with simultaneous dosing or with an interval of 12 hours. Co-administration of edoxaban at a dose of 60 mg and subcutaneous enoxaparin at a dose of 1 mg/kg led to an increase in the effect on the parameters of the analysis of thrombin formation compared to any of the drugs introduced separately. The effect was generally not additive, with the exception of the delay in thrombin formation and the time to peak. The effect on anti-FXa with the simultaneous use of both drugs was additive [103].

Candidate genes influencing the concentration of edoxaban are genes encoding key enzymes of its metabolism: *CES1*, *CYP3A4/5*, *ABCB1* [54] and, to a lesser extent, *SLCO1B1* [104].

Edoxaban and its active metabolite M4 are substrates for P-gp encoded by *ABCB1* (*MDR1*) gene and the organic anion carrier protein OATP1B1 encoded by *SLCO1B1* gene. The pharmacogenomic analysis combined genotype and concentration-time data in 458 healthy volunteers in 14 completed phase 1 studies. The SNVs effect of *ABCB1* gene (rs1045642: C3435T) and *SLCO1B1* gene (rs4149056: T521C) on pharmacokinetic parameters of edoxaban was studied. Although some pharmacological inhibitors of P-gp and OATP1B1 increased exposure to edoxaban, C3435T (rs1045642) of *ABCB1* gene, nor T521C (rs4149056) of *SLCO1B1* gene did not affect the pharmacokinetics of edoxaban. Although, a slight increase in M4 exposure was observed in carriers of minor allele C* of *SLCO1B1* gene [104].

Only a limited amount of edoxaban is metabolized by liver cytochrome P450 isoenzymes (less than 4%) [105]. Metabolites M4 and M1 are formed during the hydrolysis of edoxaban with the participation of the *CES1* enzyme encoded by *CES1* gene, while M6 is formed through metabolism with the participation of the *CYP3A4/5* isoform, encoded by *CYP3A5* gene [92]. Analysis of genomic associations showed that SNVs of *CES1* gene affect the plasma levels of dabigatran [106]. So far, no studies have been found on the effect of carriage of the studied SNVs of *CES1* gene on the pharmacokinetics of edoxaban. However, this may be promising in terms of personalized selection of DOACs.

There is probably a high risk of developing edoxaban-induced adverse reactions due to a slowdown in the metabolism of the drug in the liver when combined with drug inhibitors of the *CYP3A5* isoenzyme in homozygous carriers of non-functional alleles *CYP3A5*. Thus, in patients belonging to the group of non-expressing *CYP3A5* (homozygous carriers of the above non-functional alleles), dosing of edoxaban should be calculated with caution and requires monitoring of the risk of bleeding. Co-administration of edoxaban with other drugs metabolized with the participation of the isoenzyme *CYP3A5* should be avoided in non-expressors, including antipsychotics (olanzapine), antiestrogens (tamoxifen), antineoplastic (irinotecan, docetaxel, vincristine), immunomodulatory agents (tacrolimus), antiplatelet agents (clopidogrel), antihypertensive agents (nifedipine, amlodipine, felodipine, verapamil), antiviral (indinavir, nelfinavir, ritonavir, saquinavir), HMG-CoA reductase inhibitors (atorvastatin), antibiotics (clarithromycin), steroids (testosterone, estradiol, progesterone and androstenedione), antimalarial drugs (mefloquine, artemether, lumefantrine) [107].

6. Conclusion

The results carried out to the present fundamental and clinical studies of DOACs studies demonstrate an undeniable the influence of genome changes on the

pharmacokinetics and pharmacodynamics of DOACs. However, the studies need to be continued. There is a need to plan and conduct larger studies in various ethnic groups with the inclusion of sufficient associative genetic studies of the number of patients in each of the documented groups treatments with well-defined phenotypes. Additional work needed to translation of research results into real clinical practice using results of pharmacogenetic testing and taking into account genomic variations for selection DOACs, their starting and target dosages, which is especially important when the need for long-term pharmacotherapy.

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