Review

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Pharmacogenetics of novel oral anticoagulants: a review of identified gene variants & future perspectives

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Novel oral anticoagulants (NOACs) are becoming a therapy of choice in everyday clinical practice after almost 50 years during which warfarin and related coumarin derivatives were used as the main anticoagulants. Advantages of NOACs over standard anticoagulants include their predictable pharmacodynamics and pharmacokinetics, stable plasma concentrations and less drug–drug and food–drug interactions. However, pharmacogenetics has its place in administration of NOACs, as considerable interindividual variations have been detected. In this review, previous findings in pharmacogenetics of dabigatran, rivaroxaban, apixaban and edoxaban are summarized, along with recommendations for studying genes encoding metabolically important enzymes for four selected NOACs. Future directions include identification of clinically relevant SNPs, and change in optimum dosage for patients who are carriers of significant variants.

First draft submitted: 28 November 2017; Accepted for publication: 25 January 2018; Published online: 16 May 2018

Keywords: anticoagulation • apixaban • dabigatran • edoxaban • novel oral anticoagulants • pharmacogenetics • rivaroxaban

Novel oral anticoagulants

Novel oral anticoagulants (NOACs), also termed direct oral anticoagulants (DOACs), are being developed for the treatment and prevention of blood clots after almost 50 years of continuous usage of warfarin as the major anticoagulant regimen [1,2]. When compared with warfarin, which inhibits the synthesis of vitamin-K-dependent coagulation factors II, VII, IX, X and proteins C and S, NOACs are inhibiting a single targeted member of the coagulation cascade without having side effects on the remaining coagulation factors [1,3]. NOACs are used for the treatment of non-valvular atrial fibrillation (NVAF), for the treatment or prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as after a major orthopedic surgery, such as total hip or knee replacement [1].

The importance of proper treatment of atrial fibrillation (AF) is best emphasized by noting that according to the European Society of Cardiology, approximately 3% of adults at the age of 20 or older experience the disease. The risk factors for occurrence of AF include older age, hypertension, heart failure, obesity, diabetes or concomitant conditions such as chronic kidney disease, valvular heart disease and coronary artery disease [4]. On the other hand, PE is approximated to occur in 100–200 per 100,000 people [5].

Both vitamin K antagonists (VKAs) and NOACs are found to be effective in stroke prevention in AF. In a study that randomized 42,411 patients to NOAC therapy and 29,272 to warfarin, it was found that NOACs were capable of decreasing the incidence of stroke or systemic embolic events by 19% when compared with warfarin. In addition, NOAC patients had a 10% lower mortality rate and 50% less frequent intracranial hemorrhage

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when plotted against the warfarin study group, while the frequency of gastrointestinal hemorrhage was lower in warfarin-treated patients [4].

When compared with warfarin and other previously developed nonspecific anticoagulants, NOACs have several advantages including a wider therapeutic range and predictable active ingredient pharmacokinetics and pharmacodynamics, and thus avoiding frequent laboratory monitoring of international normalized ratio (INR) and other parameters. In addition, NOACs are known for not being prone to many drug–drug and drug–food interactions, mainly since they are not completely dependent on cytochrome P450 and vitamin K intake, respectively, which also contributes to these drugs having less side effects when compared with warfarin [1,3]. Previous clinical trials have demonstrated that in comparison to warfarin or antiplatelet drugs, NOACs exhibit reduced total mortality rates and less frequent cardiovascular mortality, intracranial bleeding and overall bleeding incidence [6].

The most frequent side effect associated with NOAC therapy is bleeding in case of overanticoagulation. However, the majority of mild bleeding events, even those that have clinical significance, are easier to control and treat as NOACs have a much shorter half-life when compared with other anticoagulants and are likely to be completely removed from the body within a day after taking the last dosage. Another important parameter that must be considered when initiating therapy with NOACs is renal and hepatic function of the patient due to the routes of metabolism and excretion of NOACs [1].

Four NOACs currently approved for clinical usage are dabigatran, rivaroxaban, apixaban and edoxaban, and these medications are discussed in the present review. The aim of this article is to give an overview of pharmacokinetics and pharmacodynamics of the previously mentioned four NOACs, and also the conditions for which treatment with these drugs is approved for clinical use and references to the pivotal studies and clinical trials that preceded the approval of these drugs for patient use. The main purpose of this paper is to summarize previous research on pharmacogenetics of dabigatran, rivaroxaban, apixaban and edoxaban, as well as to give future directions for personalization of NOAC therapy, that is, to tailor the anticoagulation therapy according to the patient's genetic background [7]. As in other fields of modern-day medicine, pharmacogenetic research on anticoagulation is mostly based upon genome-wide association studies (GWAS) that have a goal of connecting genetic variants (in this case, SNP markers) to a specific phenotype expressed by the patient, usually the differential response to the drug, with the ultimate goal of applying the translational medicine approach to anticoagulant therapies [8].

Included in this review are all peer-reviewed original research articles, review papers and case studies collected from PubMed, PubMed Central, ResearchGate and Google Scholar. Databases have been searched by the following key terms: 'dabigatran', 'rivaroxaban', 'apixaban', 'edoxaban', 'pharmacogenetics', 'pharmacogenomics', 'NOACs', 'DOACs', 'gene', 'SNP' and 'polymorphism'. In order to include a paper in the present review, the following inclusion criteria had to be fulfilled: an article is published in English language, its subject is any of the four study drugs, it is presenting the results of a clinical trial on either healthy individuals or patients or an *in vitro* study on human cell lines, appropriate genotyping and statistical analyses have been performed and the results are clearly stating whether a positive correlation between the genetic polymorphism and drug metabolism in an individual or a sample has been established. All articles presenting *in vitro* or *in vivo* studies in nonhuman models have been excluded, along with the articles that have not been peer-reviewed by the relevant scientific journal and whose methodology does not allow for clear and accurate interpretation and discussion of the obtained results.

Dabigatran

Dabigatran, delivered to patients in the form of dabigatran etexilate (DABE) that is rapidly hydrolyzed to dabigatran by P-glycoprotein (P-gp), is serving as a direct inhibitor of both free and clot-bound thrombin (factor II) activity. Thrombin activity is of the primary importance in human coagulation system as it activates fibrinogen (factor I), as well as factors V and XI of the coagulation system [9,10]. Dabigatran also inhibits conversion of fibrinogen to fibrin, a process carried out by thrombin as the last step in the coagulation cascade [9]. Inhibition of thrombin activity by dabigatran does not include inhibition of thrombin generation and is specific, meaning that it does not affect other coagulation factors [11].

In the main clinical trial that evaluated the efficiency and safety of dabigatran usage in patients with AF, either 150 mg (high dose) or 110 mg (low dose) of dabigatran was given to patients and compared with the performance of warfarin given in a therapy that keeps the patients subjected to warfarin therapy within the INR range of 2–3. High dose of dabigatran reduced stroke and systemic embolic events by 35%, while the rate of bleeding events was not statistically different from that of warfarin patients. A low dabigatran dose reduced stroke, and systemic embolism is a noninferior way when compared with warfarin, while bleeding rates were decreased by 20%. Furthermore,

hemorrhagic stroke and intracranial hemorrhage were less frequent in both dabigatran groups, while high dose dabigatran increased gastrointestinal bleeding by 50% when compared with warfarin. The results of this study led to approval of dabigatran for the prevention of stroke and systemic embolism in patients with AF [12].

The studies after which dabigatran was approved for the treatment of venous thromboembolism (VTE), comprising either DVT or PE, or both, were RE-COVER and RE-COVER II trials that replicated each other's results. Out of 2539 patients participating in RE-COVER trial, 21% of them had PE, while 9.6% had both DVT and PE. After receiving parenteral anticoagulation for 10 days, patients were randomized to dabigatran and warfarin groups. Dabigatran was noninferior to warfarin in terms of efficacy and major bleeding events were equally frequent in both groups. However, the frequency of any bleeding event was lower in dabigatran group [13].

In order to assess the efficacy and safety of dabigatran in prevention of VTE following total hip arthroplasty (THA), 150 or 220 mg dabigatran were compared with 40 mg enoxaparin therapy in RE-NOVATE and RE-NOVATE II trials. The results of these two studies imply that the risk of VTE and all-cause mortality, as well as the frequency of bleeding events were similar in the study groups. However, the frequency of major VTE or VTE-related deaths was significantly lower in dabigatran group [14]. At last, RE-MODEL trial involved 2076 patients undergoing total knee replacement in which dabigatran was compared with enoxaparin using the same study design as in two previously mentioned trials. The results of this study imply that dabigatran is at least as efficient and safe as enoxaparin in prevention of VTE following total knee replacement [15]. Dabigatran is now approved for usage in both of these conditions by EMA and US FDA [10].

The drug is metabolized by plasmatic esterases, instead of interacting with cytochrome P450 [10]. Dabigatran peak plasma levels are reached within 2 h of ingestion, while drug half-life in adult patients is 14–17 h [9,11]. Advantages of dabigatran compared with previously used anticoagulants include its predictable and constant plasma concentrations, relatively short half-life, low bioavailability and rapid excretion.

Due to 80% of digested drug being excreted in non-metabolized form via urine and 20% in metabolized form through stool, the drug is avoided in patients with impaired kidney function, and especially in patients with end-stage renal disease [10]. It has also been found that plasma concentrations of dabigatran tend be higher in women, elderly patients and those with body weight under 50 kg and over 100 kg [11]. When it comes to drug–drug interactions, dabigatran might be differentially influenced by efflux transporter P-gp inducers or inhibitors, as well as by antiplatelet drugs, such as aspirin. Identified risks in the course of dabigatran therapy for the treatment of VTE include the possibility of bleeding events, contraindication in patients with mechanical heart valves, either with or without AF [11], and an increased frequency of myocardial infarction when compared with warfarin during the course of the therapy [16].

In case of bleeding or urgent surgical procedure, dabigatran therapy is stopped and supportive measures, such as dialysis are administered. Additionally, administered substances might include prothrombin complex concentrates (PCCs), activated PCCs (aPCCs) and recombinant activated factor VII (rFVIIa) [17]. Idarucizumab has recently been approved for usage as direct dabigatran antidote and it is a humanized monoclonal antibody fragment that directly binds dabigatran reducing its anticoagulant activity and decreasing its availability in the body. In addition, idarucizumab is dabigatran-specific, meaning that it does not interfere with other members of coagulation cascade and does not have coagulation-promoting properties itself. Possibility of potentially impairing medical conditions, such as liver or kidney disease, should be considered prior to reversing dabigatran activity using idarucizumab [18].

Dabigatran pharmacogenetics

The first publication to discuss dabigatran pharmacogenetics has been published in 2011 by Cavallari and colleagues. The candidate genes identified in this study include *ABCB1* gene, which is encoding for P-gp as DABE is a substrate for this enzyme, as well as thrombin active site which is the point of attachment of dabigatran to thrombin. Additionally, it is pointed out that dabigatran is generated from its prodrug using esterases and not cytochrome P450, implying that CYP genes are not related to dabigatran pharmacogenetics [19].

The first evidence of specific SNP markers that might be related to dabigatran interindividual variability was offered by Pare and colleagues in 2013. Apart from *ABCB1*, liver esterase *CES1* has also been studied since it is involved in conversion of DABE to dabigatran in the liver. In the study, 1490 patients of European origin were subjected to a genome-wide analysis which involved the analysis of 551,203 SNPs, followed by the analysis of polymorphisms of the two abovementioned genes involved in dabigatran metabolism. The most influential SNP detected was rs2244613 in intronic region of *CES1* gene (G>T transversion) [20] in which heterozygous individuals had 15% lower trough dabigatran concentration in plasma, while patients homozygous for minor allele are expected

10.2217/pme-2017-0092

to have 28% lower concentrations according to the study results. Other statistically significant *CES1* SNP was another marker from intronic region, rs8192935 (C>T transition), that was associated with a 12% decrease in peak plasma concentration of the drug per minor allele present in the genotype. On the other hand, intronic *ABCB1* SNP rs4148738 (G>A transition) was associated with 12% increase in peak concentration per minor allele detected. All three SNPs are shown to influence dabigatran bioavailability, although all of them are present in intronic regions of their respective genes. It is speculated that this phenomenon is explainable by the fact that as they are located in close proximity of other, probably still unidentified exonic SNPs, these three markers are in linkage disequilibrium with the SNPs from the coding region, thus indirectly influencing other variants and contributing to interindividual variations in response to dabigatran [21]. Carrying minor allele(s) on rs2244613 conferred with a decreased risk of any type of bleeding while on dabigatran therapy, while it was not correlated with ischemic events. Other two SNPs were not connected to either bleeding or risk of ischemic events [22–25].

In the study of 52 patients on dabigatran therapy treated for NVAF from New Zealand, the impact of three SNPs has been investigated to assess their importance as predictive markers of the optimum drug dose that should be administered to the patients. Patients with homozygous wild-type (wt) genotype were assigned value 1, while those with heterozygous genotype or with two minor alleles were assigned value 2. The results imply that neither of three analyzed SNPs (rs2244613, rs4122238 and rs8192935, all from *CES1* gene intronic regions) was predictive of personalized DABE dose for the study patients [26].

In yet another study of 92 Caucasian outpatients with the diagnosis of AF, the only significant positive correlation was observed between *CES1* SNP rs8192935 and decreased dabigatran trough levels. The other two SNPs were not correlated with peak or trough concentrations of the drug [27]. The conclusion that another intronic SNP influences patient's response to dabigatran is again justified by the probability of linkage disequilibrium due to these three SNPs being clustered in one genomic region of chromosome 16 [20].

Two *ABCB1* SNPs, rs2032582 (also known as G2677T/A or Ala893Thr, located in exon 21) [28] and rs1045642 (C3435T change in exon 26) [28,29] are common in Caucasians and are related to differential P-gp expression and activity *in vitro*. The study by Gouin-Thibault and colleagues was performed on 60 healthy French males with balanced distribution of three possible genotypes (20 subjects wt, 20 heterozygous and 20 homozygous mutated genotypes). Due to linkage disequilibrium, the two SNPs were studied together as a single haplotype rather than separately. When compared with wt individuals, heterozygous and homozygous mutated individuals had 13 and 33% higher plasma peak values, respectively. Although both SNPs are contributing to the decrease of P-gp activity *in vivo* and *in vitro*, the clinical importance of the reported variants on dabigatran pharmacokinetics has not been observed [30].

In a recent *in vitro* study, 104 normal human liver samples of individuals of different racial backgrounds have been investigated for three *CES1* SNPs, namely rs2244613, rs8192935 and rs71647871 (or G428A, also referred to as G143E, which is the-loss-of-function *CES1* variant) [31,32]. The results imply that G143E mutations are related to the decrease in the activation level of DABE, but the difference between wt and mutant allele carriers did not reach statistical significance. However, when the results were normalized to individual differences in *CES1* expression levels, the difference in DABE activation between mutant allele carriers and noncarriers has become significant thus implying the importance of *CES1* gene expression levels in addition to identified SNP variations. The other two SNPs were found to be unrelated to DABE activation and *CES1* expression and activity. In addition, it has been found that gender is an important determinant of DABE activation as *CES1* is more expressed in female subjects than male subjects, which contributes to higher exposure of females to dabigatran when compared with males. It is important to note that more than 2000 *CES1* genetic variants have been identified so far and their potential impact on dabigatran is still to be studied in detail [32]. A summary of all relevant SNP variants and their impact on dabigatran therapy is given in Table 1.

Rivaroxaban

Rivaroxaban is the first direct factor Xa inhibitor approved for use in prevention of VTE in patients undergoing elective knee or hip replacement surgery, as well as for the prevention of stroke and systemic embolism in patients with NVAF. The drug is highly selective, does not inhibit activity of already existing thrombin molecules and has high plasma protein binding properties, thus not being easily removed via dialysis [34,35]. It is capable of binding free, as well as prothrombinase-bound and clot-bound, factor Xa, thus inhibiting thrombin formation in the coagulation cascade. The bioavailability of rivaroxaban is high being in the range of 80–100%, its peak plasma concentration

Table 1. The summary of SNP markers that were previously found to be associated with pharmacodynamics and/or pharmacokinetics of three novel oral anticoagulants, namely dabigatran, rivaroxaban and apixaban.

NOAC	SNP ID	Gene	DNA polymorphism	Study population	Treatment indication	PK/PD effects	Effect on clinical outcomes	Ref.
Dabigatran	rs2244613	*CES1* intronic region	G>T	European ancestry	AF	Decrease in drug trough concentration Changes in bioavailability, volume of distribution and clearance	Smaller risk of bleeding while on dabigatran therapy	[24]
	rs8192935		C>T	European ancestry	AF	Decrease in drug peak concentration Changes in bioavailability, volume of distribution and clearance	No statistically significant effects observed	[24]
				Italian	AF	Decrease in dabigatran trough levels	Analysis not performed	[27]
	rs71647871 (G143E)	*CES1* exonic SNP	G428A	*In vitro* study of human liver samples; mainly Caucasian origin	Normal samples	Loss-of-function variant Decrease in the activation level of DABE *in vitro*	N/A	[32]
	rs4148738	*ABCB1* intronic region	G>A	European ancestry	AF	Increase in drug peak concentration Changes in bioavailability, volume of distribution and clearance	No statistically significant effects observed	[24]
	Haplotype rs2032582 (Ala893Thr) + rs1045642	*ABCB1* exons 21 and 26, respectively	G2677T/A and C3435T, respectively	French Caucasian	Healthy individuals	Clinically insignificant increase in plasma peak levels	No clinically relevant complications recorded	[30]
Rivaroxaban	rs2032582	*ABCB1* exon 21	c.2677G>T	French Caucasian	Healthy individuals	Clinically nonsignificant increase in drug plasma peak level	No clinically relevant complications recorded	[30]
				A case study of an elderly Swiss male patient	Cardioembolic strokes and AF	Evidence of impaired drug clearance Increase in drug trough level	Suspected GI bleeding	[33]
	rs1045642	*ABCB1* exon 26	c.3435C>T	French Caucasian	Healthy individuals	Clinically nonsignificant increase in drug plasma peak level	No clinically relevant complications recorded	[30]
				A case study of an elderly Swiss male patient	Cardioembolic strokes and AF	Evidence of impaired drug clearance Increase in drug trough level	Suspected GI bleeding	[33]
Apixaban	rs4148738	*ABCB1* intronic region	G>A	Italian Caucasian	AF	Decrease in drug peak concentration Statistically nonsignificant decrease in trough concentration	Analysis not performed	[21]

AF: Atrial fibrillation; GI: Gastrointestinal; NOAC: Novel oral anticoagulant; PD: Pharmacodynamic; PK: Pharmacokinetic.

10.2217/pme-2017-0092

is reached within 2–4 h, while the half-life of active ingredient is 7–11 h in young patients and 11–13 h in older patients [34].

The ROCKET-AF trial had a purpose of comparing efficacy and safety of rivaroxaban in prevention of stroke in AF patients in comparison to warfarin. This study, which was conducted on 14,264 patients, compared 20 mg rivaroxaban once daily to adjusted warfarin therapy. The results implied no significant differences between the groups in terms of the frequency of stroke and bleeding events in general. However, the frequency of fatal and intracranial bleeding was significantly lower in rivaroxaban group [36].

In order to investigate rivaroxaban therapy in VTE, two separate studies, namely EINSTEIN-DVT and EINSTEIN-PE were conducted in which rivaroxaban therapy was compared with enoxaparin/VKA groups. The results have shown that rivaroxaban had noninferior performance in terms of efficacy and safety compared with the traditional therapy. The potential for improved performance of rivaroxaban in prevention of major bleeding events was recorded in EINSTEIN-PE study [37,38]. Following the results of these two trials, rivaroxaban has also been approfved for the treatment and prophylaxis of recurrent VTE.

The studies that assessed rivaroxaban performance in thromboprophylaxis following total knee or hip replacement include RECORD 1, 2 and 4 trials (for THA) and RECORD 3 (for total knee arthroplasty, TKA). The results of these studies imply that rivaroxaban outperformed enoxaparin in prevention of symptomatic VTE or DVT, but not PE. When it comes to the safety of rivaroxaban therapy, it should be emphasized that this therapy was associated with an increase in major bleeding events, while the difference between the two therapies in terms of mortality rates, wound infection and clinically relevant nonmajor (CRNM) bleeding was not detected [39].

The drug is metabolized by several cytochrome P450 enzymes, including CYP3A4/5 and CYP2J2, as well through CYP-independent mechanisms [35]. A third of the drug is excreted in non-metabolized form through urine with the activity of P-gp and *BCRP*, while the other two thirds are metabolized in the liver with half of the metabolized product being excreted through kidneys and the other half through the hepatobiliary tract. The possibility of drug–drug interactions is noted only with CYP3A4 and/or P-gp inducers or inhibitors. Rivaroxaban metabolism is not affected by gender, ethnicity and body weight, while its clearance is in part compromised in elderly patients and individuals with renal and liver function impairment [34,35].

As shown in an earlier *in vitro* study, in case of bleeding, rivaroxaban activity is reversed using aPCC and rFVIIa, while PCC does not seem to improve the overall condition in case of a bleeding event [40]. Rivaroxaban antidote andexanet alfa, which is currently passing through clinical trials, was shown to decrease drug activity by 92% in the study group versus 18% patients who received placebo, along with a statistically significant decrease in concentration of unbound rivaroxaban and successful restoration of thrombin generation. Andexanet alfa is a recombinant modified human factor Xa decoy protein that is capable of binding factor Xa inhibitors in their active site and sequestering them in the vascular space. Neutralizing antibodies against andexanet or antifactor X or factor Xa are not getting developed in the course of reversal therapy. Due to a relatively short half-life of andexanet of 1 h, the levels of rivaroxaban activity, thrombin generation and unbound rivaroxaban are returning to the values seen in the placebo group within 1–3 h [41].

Rivaroxaban pharmacogenetics

In the first reports on possible genes that might be modulating rivaroxaban activity *in vivo*, the main genes that were highlighted are *CYP3A4/5, CYP2J2* and P-gp system [19,42]. For a more exhaustive list of genetic variants that have a potential to be exploited in rivaroxaban pharmacogenetic studies, we are recommending consulting a review by O'Connor and colleagues (2017) [43].

Two *ABCB1* SNP markers rs2032582 and rs1045642 have been investigated in terms of their role in rivaroxaban metabolism in patients. Compared with individuals with wt haplotype, those who were heterozygous or homozygous for mutant alleles had 18 and 10% higher plasma peak levels, respectively. These results indicate that the two markers have no clinical significance in the course of rivaroxaban therapy, as previously also shown on an example of dabigatran [30].

A case study of a 79-year-old male who was receiving rivaroxaban for the prevention of cardioembolic strokes and AF reports on the effect of two *ABCB1* markers on rivaroxaban therapy. The patient suffered from gastrointestinal bleeding and was presented with anemia. Other underlying medical conditions were Type 2 diabetes and partial renal impairment. Patient's genotypes for both SNPs (rs2032582 and rs1045642) were TT, thus making this individual homozygous for mutated alleles in both *ABCB1* markers (c.2677G>T and c.3435C>T), while *CYP3A4/5* phenotyping showed moderately decreased enzyme activity. Laboratory analyses showed evidence of

impaired rivaroxaban clearance, which in part might be influenced by moderate renal impairment observed at the time of hospitalization. On the other hand, since only a third of rivaroxaban is excreted through renal pathway and since the renal impairment was resolved as soon as four days, it is suggested that genotypes on two SNPs of *ABCB1* gene might play a role in compromised drug clearance. There are more than 100 SNPs in *ABCB1* gene region occurring at frequency higher than 5%, while two markers investigated in this study have inter-racial prevalence range of 2–90%, which points out to the fact that many other *ABCB1* variants are still to be studied (Table 1) [33].

At last, another case report announced that a 6-year-old girl with homozygous protein S deficiency has been receiving a daily dose of rivaroxaban that equals double the dose usually given to adult patients and bleeding events did not occur. Plasma analyses after thrombomodulin addition revealed a decrease in thrombin generation, while thrombin peak and velocity were unexpectedly rising. In plasma samples from patients with heterozygous protein S deficiency, similar but less pronounced effects have been observed. The results imply that patients with either heterozygous or homozygous protein S deficiency might be candidates for higher dosage of rivaroxaban to reach necessary anticoagulant effect without bleeding, as well as the major role protein S plays in thrombin peak and velocity index [44].

Apixaban

Apixaban is an oral anticoagulant drug prescribed to reduce the risk of stroke and systemic embolism in patients with NVAF, for the treatment and prevention of recurrent VTE and for prevention of VTE in patients undergoing a major orthopedic surgery of the lower limbs. It is acting as direct and selective factor Xa inhibitor, thus preventing clot formation without influencing other coagulation cascade members. This drug is capable of binding both free and clot-bound factor Xa [45,46].

In order to assess apixaban performance in stroke and systemic embolism prevention in patients with AF, the ARISTOTLE trial was conducted and its results published in 2011 [47]. Apixaban twice daily at 5 mg doses was compared with optimized warfarin therapy. According to the study results, stroke and systemic embolism events were reduced by 21% in apixaban group when compared with warfarin, in addition to lower rates of hemorrhagic stroke and intracranial bleeding. On the other hand, frequencies of ischemic stroke and gastrointestinal bleeding did not differ significantly between the groups. When it comes to overall safety of apixaban therapy, the incidence of all-cause mortality was decreased by 11%, while major bleeding was 31% lower than in warfarin [47].

AMPLIFY study compared a single-drug apixaban therapy to a composite enoxaparin/warfarin regimen in 5395 patients with acute VTE. The efficacy of apixaban was noninferior to the standard therapy, while its safety profile was improved. More precisely, major bleeding occurred in 0.6% apixaban patients versus 1.8% patients on conventional therapy, while major and CRNM bleeding together occurred in 4.3% patients in apixaban group and 9.7% patients in enoxaparin/warfarin group. Both of these results are statistically significant [48].

Three trials were evaluating the efficacy and safety of apixaban versus enoxaparin in the prevention of VTE following major orthopedic surgeries, namely ADVANCE-1 and ADVANCE-2 for TKA and ADVANCE-3 for THA. In 5407 patients undergoing hip replacement, apixaban was superior to enoxaparin in VTE prevention, with 1.4 and 3.9% patients diagnosed with symptomatic or asymptomatic VTE in apixaban and enoxaparin groups, respectively, while bleeding rates were similar between the groups [49]. In ADVANCE-2 trial, 3057 patients undergoing knee replacement were tested with the results implying lower rates of major or CRNM bleeding, as well as lower incidence of primary outcome, comprising symptomatic or non-symptomatic DVT, nonfatal PE and all-cause death [50].

Apixaban is metabolized through cytochrome P450 3A4-related mechanisms, which includes CYP3A4 as the main metabolizer, with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2J2. Its first nonreactive metabolite is termed O-demethyl apixaban sulfate. The peak concentration of the drug in plasma is reached within 3–4 h, while its half-life is 12 h. The drug is highly protein-bound at fraction around 87% thus being nondialyzable, while bioavailability of the active ingredient is 50% for up to 10-mg dose. Around 25% of the drug is eliminated from the system in form of metabolites through urine and feces, while the plasma portion of the drug is present as unmodified apixaban, since this drug is unlikely to produce reactive metabolites. Direct renal excretion accounts for around 27% of the total drug that enters the organism [45].

Since apixaban is a substrate for P-gp and CYP3A4, taking apixaban together with P-gp or CYP3A4 inhibitors can increase its presence in plasma and chance of bleeding, while taking it with inducers of P-gp or CYP3A4 can reduce its efficacy and concentration. Apixaban is contraindicated in patients with active pathological bleeding, while more frequent monitoring is recommended in patients with extreme body weight or hepatic or renal impairment [45,46,51].

10.2217/pme-2017-0092

On the other hand, there is no proof that age or sex of the patient is clinically relevant when deciding on the therapeutic dosage of apixaban [52]. The drug should be discontinued 24 h prior to invasive procedure or urgent surgery in case of low chance of bleeding and 48 h if the probability of bleeding is high [45].

In case of bleeding, reversal measures are implemented according to the severity of the event. Usual workflow includes drug cessation, supportive measures including transfusion if necessary, as well as the addition of PCC, aPCC and rFVIIa, which were proven to be effective *in vitro* in thrombin generation and shortening bleeding time [46]. In the previously discussed study in which the effect of andexanet alfa as rivaroxaban antidote had been investigated *in vivo*, the impact of the same substance on apixaban reversal has been reported as well [41]. After andexanet alfa was given to apixaban-treated patients, antifactor Xa activity was decreased by 94% in the study group versus 21% in participants who received placebo. Additionally, the concentration of unbound apixaban decreased significantly, while thrombin generation was restored in 100% participants within 2–5 min as opposed to 11% participants in the group that received placebo [41].

The *in vivo* study of differences in pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban has yielded the conclusion that apixaban exerts less interindividual variability, as well as smaller peak-to-trough plasma concentrations of the drug, which implies that this drug has more stable coagulation mechanism. An important aspect to be considered while interpreting the study results is the fact that apixaban is delivered twice and rivaroxaban once a day in anticoagulation therapy [53].

Apixaban pharmacogenetics

In a review by Sweezy and Mousa (2014), it was emphasized that apixaban is metabolized by CYP3A4, CYP-independent pathway and via renal extraction and that CYP-related genes might be good candidates for studying apixaban pharmacogenetics. Two genes that also might be involved in its regulation are *SULT1A1* and *SULT1A2*, which are sulfotransferases responsible for conjugating apixaban into O-demethyl-apixaban [42].

In a study of 80 outpatients of Caucasian origin, *ABCB1* intronic SNP rs4148738 (G>A) has been found to influence peak but not trough plasma concentrations of apixaban. In heterozygous and homozygous mutated genotypes (GA and AA, respectively), peak concentrations of apixaban were decreased for 26 and 32%, respectively, which is statistically significant. On the other hand, 26 and 18% decrease in trough concentrations in GA and AA genotype carriers was not found to be statistically significant. Overall, 6% of the difference in response to drug has been assigned to rs4148738 variations and 8.7% to gender [21]. Therefore, after concluding that this SNP lacks clinical relevance in response to dabigatran therapy, it has been successfully linked to apixaban bioavailability and clearance (Table 1).

Edoxaban

Edoxban is another direct factor Xa inhibitor delivered as an oral therapy once a day in either 30- or 60-mg doses. As of 2015, it has been approved in the USA and Japan for the prevention of stroke and systemic embolism in patients with NVAF and for the VTE treatment. In addition, it has also been approved for the prevention of VTE following total knee or hip replacement in Japan. The drug has 62% bioavailability, while a 35% fraction is excreted through the kidneys. Its half-life is in the range of 8–10 h, while peak plasma concentration is achieved within 1–2 h after ingestion [54,55]. Although edoxaban has notably less drug–drug interactions than other NOACs, interactions with P-gp inhibitors were proven, as these drugs are capable of causing increased plasma concentrations of edoxaban, while P-gp inducers were shown to decrease edoxaban concentration [56,57]. In addition, food intake, age, gender and ethnicity have no influence on drug pharmacological profile. However, in patients with body weight below 60 kg, increased edoxaban exposure is indicated, while patients with renal impairment have been found to tolerate 15-mg daily doses well [58,59]. Another advantage of edoxaban over standard VKA-based anticoagulation therapy is its relatively low plasma protein-binding level of around 55%, which is also lower than that of other factor Xa inhibitors, meaning that patients on hemodialysis will not experience interactions of the regimen with edoxaban protein binding, clearance and exposure [59].

Phase III clinical trials tested the performance of edoxaban in three different indications, namely AF, treatment of diagnosed VTE, as well as prevention of VTE following major orthopedic surgeries. In the first one named ENGAGE AF-TIMI 48, edoxaban performance in stroke prevention in two different doses (30 and 60 mg) was compared with dose-adjusted warfarin in patients with AF. Depending on the dose administered, edoxaban was found to be either superior or noninferior to warfarin therapy in terms of stroke prevention, the risk of myocardial infarction, as well as bleeding rates. Hokusai-VTE is a trial that compared low molecular weight

heparin/edoxaban to warfarin coupled to low molecular weight heparin therapy. The results implied that edoxaban after the initial heparin treatment was noninferior and produced significantly less bleeding events when compared with heparin/warfarin regimen. At last, the studies STARS E-3, STARS J-4 and STARS J-5 were investigating the efficacy of edoxaban in total knee replacement, hip fracture surgery and total hip replacement, respectively. The major conclusion from all three STARS studies is that edoxaban was superior in VTE prevention when compared with enoxaparin, while it was associated with a similar risk of bleeding when compared with the same control drug [59].

Around 4% of edoxaban is metabolized through cytochrome P450, while its intestinal transport is mediated by P-gp efflux transporter [59]. CYP3A4/5 is producing M6 from edoxaban through biotransformation, while the rest of its metabolism is mediated by CES1, which is hydrolyzing the drug to produce metabolites M1 and M4 [43].

In 2014, there were no approved antidotes for edoxaban, with research suggesting that changes in prothrombin time caused by edoxaban can be reduced via the activity of PCC, aPCC and rFVIIa [59]. According to the latest reports, andexanet alfa is considered to be approved as an edoxaban antidote by EMA, while four-factor PCC is now used to reverse the effects of edoxaban within a 30-min frame after the drug delivery [56]. In addition, another antidote is currently being developed. PER977 (aripazine) is a synthetic molecule directly binding to factor IIa and Xa inhibitors through hydrogen bonding without procoagulation properties. When given 3 h after the last edoxaban dose, PER977 was capable of returning blood clotting time to less than 10% above the baseline within 10 min after its administration, as opposed to placebo drug that took 12–15 h to achieve the same effect. The antidote effects were observable for 24 h [60,61].

Edoxaban pharmacogenetics

To the best of our knowledge, no studies were conducted regarding edoxaban pharmacogenetics that would possibly identify SNP markers that could be relevant for edoxaban metabolism and transport. However, according to the previously published information, candidate genes for edoxaban-related GWAS could be those encoding for CES1, CYP3A4/5, as well as P-gp [43,59].

On the other hand, the absence of correlation between edoxaban therapy response and SNP variants was assessed in two previous studies. In the first study, 14,348 patients from ENGAGE AF-TIMI 48 trial diagnosed with NVAF for at least 12 months were characterized as normal, sensitive or highly sensitive warfarin responders based on *VKORC1* and *CYP2C9* genotypes. While the percentage of patients experiencing major or CRNM bleeding events increased with warfarin sensitivity in the first 90 days, those effects diminished after 90 days of warfarin therapy due to dose adjustment. On the other hand, there were no statistically significant differences in the frequency of any bleeding event between the patient groups when they received either low (30 mg) or high dose (60 mg) of edoxaban, thus implying that gene polymorphisms important for warfarin metabolism do not affect the patient's response to edoxaban. Additionally, lower hazard ratios for bleeding events in edoxaban against warfarin were scored in the first 90 days in both groups, namely 0.90 for high dose and 0.70 for low dose edoxaban [62].

The second study was a subanalysis from Hokusai-VTE trial, in which 3956 patients diagnosed with VTE were analyzed. Out of those, 1978 were given heparin/warfarin therapy and genotyped for *VKORC1* and *CYP2C9* alleles in order to divide them into normal, sensitive and highly sensitive responders. When compared with wt individuals, sensitive and highly sensitive responders ended up with lower warfarin doses with the goal of keeping INR between the values of 2 and 3, had their therapy discontinued earlier, experienced more bleeding events and were overanticoagulated for a prolonged period of time. On the other hand, edoxaban-treated patients received a 60-mg dose once daily, with a dose reduction to 30 mg in case that patient's body mass was below 60 kg, or creatinine clearance rate was 30–50 ml/min, or a patient was receiving any P-gp inhibitor as a concomitant therapy. Due to smaller number of individuals classified as sensitive and highly sensitive responders, and consequently, a low number of major bleeds in these two separate categories, the comparison of warfarin and edoxaban has been performed on a two-bin basis, namely normal and sensitive warfarin responders. When the study participants were stratified in this way, it has been shown that warfarin-sensitive patients experienced more bleeding events when given warfarin than when given edoxaban as their anticoagulation therapy [63].

Conclusion & future perspective

Pharmacogenetics, a novel approach in modern clinical practice, means to tailor patient's therapy according to their genotype. NOACs, although characterized by predictable pharmacodynamics and pharmacokinetics, as well as stable plasma concentrations and relatively short half-life, still exhibit a certain degree of interindividual variability.

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Due to that, GWAS of genes of interest should be designed and executed with the goal of identifying relevant SNP variations that might be implemented in a NOAC administration algorithm. For dabigatran, factor IIa inhibitor, candidate genes would be *CES1, CES2* and *ABCB1*, since DABE is a substrate for these enzymes. When it comes to factor Xa inhibitors rivaroxaban, apixaban and edoxaban, *ABCB1* gene is again one of the main candidates, as it is encoding P-gp which is recognizing all study pharmaceuticals as its substrates. In addition, CYP-related enzymes, such as *CYP3A4* and *CYP2J2* would be other suitable candidates for personalization of antifactor Xa therapy.

Executive summary

Novel oral anticoagulants

- Novel oral anticoagulants (NOACs) are being developed as an alternative to standard nonspecific antiplatelet and vitamin K antagonist therapy.
- NOACs are characterized by stable pharmacokinetics and pharmacodynamics, predictable peak and trough plasma levels, less drug–drug and food–drug interactions and do not require constant international normalized ratio measurement.
- Currently, four NOACs are approved for clinical usage, namely dabigatran, rivaroxaban, apixaban and edoxaban.

Dabigatran

- Dabigatran is a direct factor II inhibitor metabolized by P-glycoprotein and plasmatic esterases instead of interacting with cytochrome P450.
- Idarucizumab is clinically approved dabigatran antidote.
- Several SNPs in both exons and introns of genes *CES1* and *ABCB1* have been found to regulate peak and trough plasma concentrations of dabigatran, as well as activation level of dabigatran etexilate and chance of bleeding events.

Rivaroxaban

- Rivaroxaban is direct factor X inhibitor approved for different clinical applications.
- The drug is metabolized through both CYP-dependent and CYP-independent metabolism.
- Two *ABCB1* SNPs have been analyzed in terms of correlation with the drug plasma levels, but clinically significant changes have not been detected so far.

Apixaban

- Apixaban is another direct factor X inhibitor approved for clinical use and metabolized by CYP-dependent and CYP-independent metabolism.
- The most recent advances in NOAC pharmacogenetics are related to apixaban.
- So far, single *ABCB1* SNP has been correlated with apixaban plasma concentrations.

Edoxaban

- Edoxaban is a direct factor X inhibitor which exhibits less drug–drug and food–drug interactions, as well as highly stable pharmacokinetics and pharmacodynamics.
- While only 4% of the drug is metabolized through CYP mechanism, the rest of it is processed by P-gp and CES1 protein.
- Currently, there are no studies reporting on genetic variants that might influence patient's response to edoxaban therapy and predict optimal dose.

Conclusion & future perspective

- Although NOACs exhibit less interindividual variability, genome-wide association studies are of the primary importance in translational medicine and personalization of anticoagulation therapy.
- More detailed studies of SNPs and linkage disequilibrium in genes encoding for cytochrome P450 complex, P-glycoprotein and plasmatic esterases are to be undertaken in order to detect novel genetic variants influencing patient's response to NOAC therapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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