Review Article

A Review of Pharmacogenetics of Anticoagulant Therapy: Heparins, Rivaroxaban, Apixaban, and Dabigatran

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Abstract

Variances in the patients' outcomes have been a well-documented challenge in anticoagulant therapy. A clinical encounter with a thromboembolic or a hemorrhagic event, due to subtherapeutic or adverse effects of an anticoagulant, is often managed by switching the anticoagulant agent into another, which is more specific and direct-acting. This management approach is usually associated with a financial burden. Additionally, the certainty of achieving better efficacy and safety profile is still questionable. Genetic variants affecting the protein sites that are involved in the anticoagulant pharmacokinetic and pharmacodynamics interactions have been suggested to contribute to the variability in the response to anticoagulant therapy. The current work reviewed the studies investigating the response variability associated with the anticoagulant therapy (heparins, rivaroxaban, apixaban, and dabigatran) and the potential pharmacogenes contributing to such response variability. Several genetic polymorphisms were reported as potential contributors to variances in response to anticoagulant therapy and were associated with adverse events. A link has been proposed for heparin resistance with single nucleotide polymorphisms (SNPs) of the anti-thrombin-encoding gene (*SERPINC1*) as well as heparin-induced thrombocytopenia with human leukocyte antigen (HLA) variant allele (*HLA-DRB3*01:01*). Several investigations also remarked variations in the serum drug level of direct oral anticoagulants (DOACs) that are associated with SNPs in the proteins contributing to the pharmacokinetics of the anticoagulant agent. Several studies discerned significant associations between SNPs in the *ABCB1* gene and elevations in the serum levels of rivaroxaban, apixaban, and dabigatran. Moreover, carriers of the variant genotype of the SNP (rs776746) in the cytochrome P450 3A5 enzyme-encoding gene (*CYP3A5*) had significantly higher drug levels when compared with the non-carriers. In contrast, some SNPs were reported to impart a protective phenotype to the carrier. The SNP (rs2244613) in the carboxylesterase-encoding gene (*CES1*) has been significantly associated with a decline in dabigatran trough levels and a lower risk of hemorrhage. Further investigations are essential to elucidate the extent of pharmacogenetics-based alterations in the drug levels as well as the subsequent clinical outcomes of anticoagulant therapy.

Keywords: Apixaban, dabigatran, heparins, pharmacogenetics, rivaroxaban

Introduction

Venous thromboembolism (VTE) events have been considered a leading cause of death and disability worldwide as 10 million incidents of VTE were encountered annually worldwide.[1,2]

Recently, a wide range of VTE incidents was reported among hospitalized cases with coronavirus disease (COVID-19) from 17% up to 48% in patients with a critical illness.[3,4]

Incidence rates for VTE events in Iraq were lacking in the literature for hospitalized patients.[5] Nevertheless, the patients who were identified at risk of VTE were estimated to be about 47% (n = 267/574) in a previous Iraqi study.[5]

Furthermore, the impact of the VTE condition, its long-term consequences, the financial complications due to diagnosis investigations, management medications,

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hospitalization, and routine monitoring and follow-up visits can be unduly burdening.[2] However, through dedicating healthcare efforts toward prophylaxis, thromboembolic events can be prevented, healthcare costs reduced, and eventually lives saved.[2]

Risk factors for VTE come in many guises that can be triangulated into Virchow's triad. The factors shift the hemostatic balance toward thrombosis.[6]

A VTE event often ensues from slowing the circulation, triggering endothelial, platelets, or immune system activation, or altering the levels of the prothrombotic and antithrombotic factors.[6]

The mortality rate of VTE was 30% of cases before the introduction of the anticoagulants. Anticoagulant therapy successfully controlled and prevented VTE events; however, it was associated with increasing the risk of bleeding, which by itself may result in mortality in up to 25% of the patients.[7]

Balancing the adverse and therapeutic effects of anticoagulant agents is critical in designing a safe and effective treatment plan. The anticoagulant treatment plan typically involves three-time phases: acute treatment (within 5–10 days after the VTE event onset), long-term treatment (within the 3-month period after the VTE event onset), and extended treatment (for more than 3 months after the VTE event onset).[7]

Acute VTE management involves the use of a fast-onset injectable agent such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC) agents such as rivaroxaban or apixaban.[7] VTE events requiring long-term and extended duration for the management are often treated with oral anticoagulants such as vitamin K antagonist (warfarin) or a DOAC agent.[7]

A comprehensive insight into all the drivers that contribute to the outcome variability from each anticoagulant medication is essential to improve the decision of selecting the most effective agent and to ensure the safety of management of VTE.[7]

Inter-patient variability in response to anticoagulant therapy has been well documented and in some agents more than others.[8] Generally, patients with inadequate response or who develop an adverse effect to an anticoagulant are often switched to another anticoagulant with a different mechanism of action (often more specific and direct-acting).[7]

However, an alternative anticoagulant is often more expensive, not necessarily safer, or associated with additional efficacy benefits.[7] At the same time, one of the mechanisms proposed for variability in the response to anticoagulant therapy is genetic polymorphisms of the protein sites that contribute to the pharmacokinetic and pharmacodynamic interactions of the anticoagulant agent.[8]

Thus, researching the capability of predicting the individual risk to the adverse (e.g. bleeding) or the sub-therapeutic (thrombotic) outcomes, based on the patient's genetic characteristics, merits further consideration.[8]

This study aimed to review the potential genetic polymorphisms involved in producing variability in response to some of the anticoagulant agents used in VTE patients or patients at risk of VTE.

An online search was conducted on the Google search engine multiple times to identify relevant studies to review. The keywords searched were "pharmacogenetics of" and "heparin," "rivaroxaban," "Apixaban," or "dabigatran." Review articles as well as research articles were included. Single case reports were also considered in this review. Short communications and letters to editors were excluded.

Heparins

Heparin products are a heterogeneous mixture of sulfated polysaccharide units. The length and the density of the negative charge of the saccharide chain contribute to the non-specific binding tendency of UFH to proteinaceous and cellular components, which diminish the anticoagulant activity.[9]

Therefore, UFH has several limitations such as the risk of bleeding and heparin-induced thrombocytopenia (HIT) and lack of predictable pharmacokinetic profile and clinical outcomes among different patients.[9]

Heparin resistance

Some patients were found to have a diminished response to heparin that was associated with lower heparin concentrations and reduced inhibitory effects on thrombus initiation and formation.[10]

Moreover, monitoring of activated partial thromboplastin time in such patients does not reliably correlate with heparin antithrombotic effects and it is likely preferred to monitor anti-factor Xa instead.[11]

Heparin resistance (clinically defined as the unusually high dose required to reach the monitoring target, which was combined with unsuccessful prevention or treatment of VTE events) is common in the intensive care unit (ICU), especially among patients with more profound systemic inflammation such as coronavirus 2019 disease (COVID-19) patients.[12,13]

Although infrequently, some patients may develop acquired antithrombin (AT) deficiency. Alternatively, proteins may bind to heparin during an acute phase reaction.[13] These factors may contribute to heparin resistance.

Contrarily, hypercoagulability status was invoked in some ICU patients, which was relatively overwhelming even with increasing heparin plasma concentrations, which could contribute to the development of thromboembolic

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events.[14,15] Additional well-designed studies are required to further explain the clotting tendency in these patients, despite higher levels of heparinization.[13]

Regarding pharmacogenetics, resistance to heparin could be attributed to SNPs of the AT-encoding gene (*SERPINC1*). One of the SNPs, rs2227589 (786G>A), was associated with a significant decline in AT concentrations and subsequently lower heparin anticoagulant effects. Though uncommon (up to 5% of VTE patients), this genetic variant was found to be a high-risk factor for morbidity.[8] Recognizing such patients at risk can be useful to improve the efficacy and safety of heparin therapy.[8]

Heparin-induced thrombocytopenia (HIT)

The main focus of heparin pharmacogenetics is HIT, which affects up to about 5% of patients on heparin and can be fatal in up to 30% of affected cases.[8,16]

Moreover, the risk of thromboembolic events and mortality due to HIT is even higher in patients with delayed identification and management. Patients, who are misdiagnosed, are predisposed to unnecessary anticoagulation and bleeding risk.[8]

Thus, characterization of a particular genetic variance to recognize patients at risk before UFH or LMWH therapy would be helpful.[8]

The proposed mechanism for HIT involved the activation of the platelet Fcγ receptor type IIa (FcγRIIa) due to the interaction of heparin-PF4 (platelet factor-4) complexes with IgG antibodies.

Pharmacogenetic studies investigating the effect of SNPs in the *FcγRIIa* gene did not find a significant association with HIT development. However, there were significantly higher frequencies of the homozygous mutant genotype carriers among patients with thrombotic events.[8]

The human leukocyte antigen allele (*HLA-DRB3*01:01*) has also been linked to HIT (odds ratio 2.81 [1.57–5.02], $P = 2.1 \times 10^{-4}$) [Table 1].[17]

Direct oral anticoagulants (DOACs)

Warfarin has been the mainstay anticoagulant used in the prophylaxis of thromboembolic events for many years. However, warfarin was limited by the late onset (up to72 h) and requirement of regular monitoring of the international normalized ratio, which added a financial burden.[18]

Direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban were alternatives to warfarin, which had more predictable pharmacokinetics and relatively faster onset.[18]

Achieving a balance between the risk of adverse effects and the desired therapeutic benefits can be challenging in real-life clinical decisions. Pharmacogenetic investigations to identify the genetic polymorphisms associated with an alteration in drug disposition provide a valuable insight, which helps select a treatment regimen tailored to the patient-relevant genetic profile and optimize the efficacy and safety of anticoagulant therapy.[18]

Rivaroxaban

This agent was used for treatment and prevention purposes for a variety of thromboembolic conditions. The time to achieve the highest drug level in blood is 2–4 h after oral administration.[18]

About a third of the oral dose of rivaroxaban undergoes renal clearance unchanged through P-glycoprotein (P-gp encoded by the *ABCB1* gene) and breast cancer resistance protein (BCRP encoded by the *ABCG2* gene). Another third of the oral dose is elimination by liver-metabolizing enzymes such as cytochrome P450 (CYP) enzyme family members CYP3A4, CYP3A5, and CYP2J2.[17] These clearance-mediating proteins are subjected to SNPs [Table 2].[18]

P-glycoprotein (ABCB1) gene

ATP binding cassette subfamily B member 1 (*ABCB1*) gene SNPs were investigated to evaluate their association with a variation in the pharmacokinetics of rivaroxaban. Kanuri and Kreutz's[23] review reported that *ABCB1* SNPs were significantly associated with a metabolic difference.[25]

The drug plasma level, the maximum concentration, half-life, and hemorrhage risk were higher in mutant homozygous (MHM) carriers to the haplotypes (rs2032582 and rs1045642).[19] It is likely advisable to screen for these genetic variants especially when rivaroxaban is being used

Table 1: Potential genetic polymorphisms and their corresponding phenotypes associated with the use of heparins

Heparins interaction site	Genetic variant	Corresponding phenotype
Antithrombin	*SERPINC1* rs2227589	Heparin resistance
Human leukocyte antigen (HLA)	*HLA-DRB3*01:01*	HIT (thromboembolic risk)
Platelet Fcγ-receptor	*FcγRIIa*-H131R	HIT (thromboembolic risk)
	FcγRIIIa-V158F	HIT (thromboembolic risk)

HIT = heparin-induced thrombocytopenia

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Table 2: Pharmacokinetic and pharmacodynamic variations of rivaroxaban based on genetic polymorphisms of *ABCB1* and *CYP3A4*

Gene	SNP Allelic change	Rivaroxaban level change or clinical outcome
ABCB1	rs1045642 3435 C > T	One Caucasian case report of bleeding associated with carriers of MHM (higher peak level)[19] A significant difference in PT in orthopedic post-operative Russians and patients carrying the ABCB1 3435CT genotype may need a dose change (%ΔPT ≤ 0).[20]
ABCB1	rs1128503 1236 C > T	Hemorrhage associated with MHM genotype carriers[21]
ABCB1	rs1128503 Combined haplotype (1236–2677–3455) 1236 C > T	Peak level not significantly different in French Caucasians[22]
ABCB1	rs2032582 2677 G > T/A	One case report of bleeding associated with a Caucasian "TT" carrier (higher peak levels)[19] Peak level not significantly different in healthy French Caucasians[22] Hemorrhage associated with MHM genotype carriers[23]
ABCB1	rs2032582, rs1045642 Combined haplotype (2677–3435) 2677 G>T, 3435 C>T	Peak level not significantly different in healthy French Caucasians[22]
ABCB1	rs4148738 intron: A > G	Hemorrhage associated with MHM genotype carriers[23]
CYP3A4	rs35599367 intron: C > T	Peak level not significantly different in MHM genotype Russian carriers[24]
CYP3A5	rs776746 6986 A > G	No statistically significant effect on PT variances (%ΔPT)[20]

MHM = mutated homozygous, PT = prothrombin time, TKR = total knee replacement, THR = total hip replacement

in a renally impaired patient or concomitantly with an enzyme inhibitor.[19]

The three ABCB1 SNPs (rs1045642, rs1128503, and rs2032582) were not significantly associated with a difference in rivaroxaban metabolism.[22]

In a more recent review by Raymond *et al.*,[26] it has been noted that the team of Ing Lorenzini *et al.*[25] reported a bleeding event in an MHM genotype carrier for rs2032582 and rs1045642. Consistently, Xie *et al.*[22] found a significantly higher drug peak level in these patients compared with the WT.

Sennesael *et al.*[21] analyzed the genotypes of *ABCB1* SNPs (rs1045642, rs1128503, rs2032582, and rs4148738) in three patients who developed rivaroxaban-induced hemorrhage. The patients were of heterozygous genotype for rs1128503, rs2032582, and rs4148738 SNPs, whereas the SNP rs1045642 genotyping revealed two heterozygous cases and a homozygous carrier.

Sychev *et al.*[19] studied the association of ABCB1 SNPs and prothrombin variance in patients with total hip replacement and total knee replacement receiving rivaroxaban as VTE prophylaxis. The prothrombin variance was significantly associated with the genotypes of *ABCB1* SNP (rs1045642).[20]

Breast cancer resistance protein (ABCG2) gene

The ATP binding cassette subfamily G member 2 (*ABCG2*) gene, encoding for BCRP, was also studied as another potential pharmacogenetic factor due to its involvement in intestinal absorption and renal elimination transport of rivaroxaban.[27,28]

The animal models lacking the efflux pumps (P-gp and BCRP) had significantly lower rivaroxaban elimination.[28]

The efflux (BCRP) pump activity was significantly associated with the *ABCG2* SNP (rs2231142). However, a pharmacogenetic study investigating this gene and rivaroxaban pharmacokinetics has not been conducted yet.[27]

Cytochrome P450 3A (CYP3A4, CYP3A5) gene

Sychev *et al.*[19] found no statistically significant dependence of prothrombin time variances (%ΔPT) on *CYP3A5* 6986A>G (rs776746) genetic polymorphism.[20] Furthermore, another work showed that the maximum rivaroxaban plasma level was not significantly associated with MHM haplotypes of the studied SNPs from both genes (*ABCB1* and *CYP3A4*).[24]

Sychev *et al.* concluded that another study with larger sample size is required to demonstrate statistically significant findings and advised to further include CYP2J2 and BCRP genotypes in future studies.[24]

Cytochrome P450 2J2 (CYP2J2) gene

Rivaroxaban use was not included in the context of the studies investigating the effect of SNPs in the *CYP2J* gene as most of these studies involved cardiovascular disease development.[18]

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Apixaban

Several studies indicated that apixaban, compared with warfarin, was superior in terms of cost-effectiveness. Apixaban's common indications include treatment of VTE and prophylaxis of thromboembolic complications such as stroke or post-operative VTE.[25]

The proportion of oral apixaban dose reaching the systemic circulation is 50%.[25] Apixaban undergoes transport mechanisms through P-gp and BCRP pumps and is predominantly available in circulation as unchanged form.[18,26]

Apixaban clearance involves different pathways. Renal clearance of unchanged apixaban constitutes about one-quarter of the eliminated apixaban. Hepatobiliary and intestinal clearance can also occur and contribute to the remaining elimination of unchanged apixaban as well as its metabolites.[26]

Apixaban is predominantly metabolized by hepatic CYP3A4/5 enzymes. Apixaban may also undergo O-demethylation and sulfation. The interpatient variability in apixaban pharmacokinetics was estimated to reach 30%, with 20% intra-patient variability.[26] Similar to rivaroxaban, SNPs can affect the proteins contributing to apixaban elimination [Table 3].

Sulfotransferases (or sulfomethyl transferases, *SULT*) gene

Sulfotransferases (SULT) mediate a major and potentially important pharmacogenomic metabolic pathway of apixaban.[26] O-demethyl-apixaban was found to be the main inactive metabolite.[25]

*SULT1A1*1*, *SULT1A1*2*, and *SULT1A1*3* have been identified as significant allelic variants of the sulfation enzymes with different maximum capacities to metabolize apixaban. *SULT1A*1* is the wildtype genotype (WT), and *SULT1A*3* has a lower metabolizing capacity and may moderately affect anticoagulation by apixaban. An insignificant metabolizing effect was associated with *SULT1A*2* allele.[25]

However, an association of *SULT1A1* polymorphisms with the pharmacokinetics or the clinical outcomes of apixaban therapy has not been examined yet.[26]

P-glycoprotein (*ABCB1*) gene

In 2016, Dimatteo *et al*.[32] studied the association of ABCB1 polymorphism and apixaban peak and trough levels in Caucasian patients. In comparison to the WT, the presence of mutant allele (A) for the SNP rs4148738 was significantly associated with the lower peak apixaban level (up to 32% reduction in peak concentration in the MHM genotype). This SNP has been suggested to affect both the absorption and elimination of apixaban and contributes to 6% of apixaban response variability.

Furthermore, Ueshima *et al*.[31] investigated the effect of different ABCB1 SNPs (rs1128503, rs2032582, and rs1045642) on the pharmacokinetics of apixaban [the outcome measure was trough level to dose ratio (TDR)] in Japanese patients. No significant variability in the apixaban TDR was found among the different genotypes of the three SNPs.

Lack of significant association between the genetic variants of the *ABCB1* gene (rs1045642 and rs4148738)

Table 3: Apixaban variations based on genetic polymorphisms of *ABCB1*, *ABCG2,* and *CYP3A5*

Gene	SNP Allelic change	Apixaban level change (clinical outcome not tested yet)
ABCB1	rs1128503 1236 C>T	Apixaban TDR was not significantly affected[29]
ABCB1	rs2032582 2677 G>T/A	Apixaban TDR was not significantly affected[29] Excessively elevated trough and peak apixaban levels in a Caucasian female who was of MHM genotype for the ABCB1 rs2032582 "TT," ABCB1 rs1045642, and CYP3A5 rs776746 SNPs and MHT for ABCG2 rs2231142[30]
ABCB1	rs4148738 intron: A>G	A significantly higher peak apixaban level[31] No significant variability in several parameters of apixaban pharmacokinetics (AUC, Cmax, Tmax, and half-life) among different genotypes of ABCB1 SNPs rs1045642 and rs4148738[32]
ABCG2	rs2231142 421 C>A	Apixaban TDR was significantly higher in MHM individuals[29] Excessively elevated trough and peak apixaban levels in a Caucasian female who was of MHT genotype for the ABCG2 rs2231142 and MHM genotype for the ABCB1 rs2032582 "TT," ABCB1 rs1045642, and CYP3A5 rs776746[30] The regression model expected a 10% and 33% increase in apixaban peak and trough levels in MHT and MHM genotypes of ABCG2 421 C>A, respectively[33]
CYP3A5	rs776746 intron: T>C	Apixaban TDR was significantly higher in MHT and MHM individuals[29] No significant variability in several parameters of apixaban pharmacokinetics (AUC, Cmax, Tmax, and half-life) among different genotypes of CYP3A5 SNPs rs776746[32] Excessively elevated trough and peak apixaban levels in a Caucasian female who was of MHT genotype for the ABCG2 rs2231142 and MHM genotype for the ABCB1 rs2032582 "TT," ABCB1 rs1045642, and CYP3A5 rs776746[30]

TDR = ratio of trough level to dose, MHM = mutated homozygous, MHT = heterozygous

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and apixaban pharmacokinetics was also reported by Kruykov *et al.*, which involved Russian individuals.[32]

Recently, Huppertz *et al.*[29] investigated a Caucasian female case with excessively high measurements of apixaban peak and trough levels. Among the four SNPs studied, *ABCB1* rs2032582 and rs1045642 were found to be mutated homozygous, which may have contributed to such an increase in apixaban levels.

BCRP (*ABCG2*) gene

Ueshima *et al.*[31] studied the effect of SNPs in *ABCG2* genes on apixaban pharmacokinetics and noted a significant increase in the apixaban TDR in MHM genotypes for the *ABCG2* (421 C > A) SNP.

Of the four SNPs studied, *ABCG2* 421C>A was found to be heterozygous in Huppertz *et al.*'s[29] reported case of excessive peaks and troughs of apixaban.

According to the regression results of Gulilat *et al.*'s[33] study on 358 Caucasian individuals, the MHM genotype "AA" for the *ABCG2* 421C>A SNP was expected to have a higher peak and trough apixaban level (a 33% increase in concentration) in comparison to the "CC" genotypes.

CYP3A5 gene

Individuals with mutated homozygous (MHM) genotypes for the lack-of-function genetic mutations in the *CYP3A5* gene were associated with the greatest possibility to encounter an adverse effect due to apixaban use.[18]

The presence of a functional allele (*CYP3A5*1*), whether in the WT or mutated heterozygous (MHT) presentation, is associated with the CYP3A5 enzyme expression phenotype, whereas patients, who are of MHM genotype, do not express CYP3A5 enzyme. It has been advised to utilize a cautious dosing approach in patients with the latter phenotype and monitor them for apixaban adverse effects.[18]

Ueshima *et al.*[31] underlined that in comparison to the WT, a significantly greater apixaban TDR was estimated in individuals with the MHT or MHM genotype for the non-functional *CYP3A5*3* allele.

Contrarily, Kruykov *et al.*'s study in Russian patients did not reveal a significant association between the SNPs in the *CYP3A5* gene and apixaban pharmacokinetics.[32]

In a case report in which a 75-year-old Caucasian female treated with apixaban for stroke prevention, Huppertz *et al.*[29] discovered four concurrent SNPs. The patient was found to have MHM genotypes for the *ABCB1* rs2032582, rs1045642, and *CYP3A5*3* SNPs and MHT genotype for the *ABCG2* 421C>A SNP. Moreover, the kidney function of the patient was moderately impaired. Thus, the clearance capacity was thought to have diminished in several eliminating sites, which contributed to the drug accumulation in excessive plasma concentrations.

Dabigatran

Prevention of stroke (in non-valvular atrial fibrillation patients) and post-operative VTE (in orthopedic surgery patients) are the indications for dabigatran use. Remarkable pharmacokinetic features include low bioavailability (3–7%), variable peak concentrations, and clearance through the liver glucuronidation metabolism as well as excretion by the kidneys.[23]

The efflux pump (ABCB1) can hinder the systemic availability of the dabigatran prodrug.[23] Moreover, two steps are required to activate dabigatran etexilate (parent prodrug).

The first step involves intestinal metabolism to an ethyl-ester metabolite via a carboxylesterase (CES2) enzyme.[23] After that, the hepatic carboxylesterase enzyme system (CES1) produces active dabigatran from the ethyl-ester metabolite.[23]

Dabigatran was shown to exhibit dramatically different pharmacokinetics in various patients. This could be in part attributed to the SNPs in *CES1* and *ABCB1* genes that affect the clearance pathways of dabigatran and result in interpatient variability in the drug levels [Table 4].[23]

CES1 gene

One of the characteristic SNPs in the *CES1* gene is the SNP rs2244613. A protective phenotype has been linked to this SNP.[34]

Elevated dabigatran troughs were considered to have an indicative capability of bleeding risk, and a significant association was found between lower dabigatran troughs and the *CES1* SNP rs2244613.[23]

The associations of this SNP with any bleeding and minor bleeding occurrences were also statistically significant ($P < 0.05$).[34]

Another study reported that the MHM genotypes for *CES1* SNP rs2244613 had decreased dabigatran troughs; however, the association did not reach a statistical significance.[35]

The effect of other variants in this gene such as rs8192935 (T > C), rs71647871 (G > A), and rs2244613 (C > A) on dabigatran pharmacokinetics has also been documented.[20,35,36] These SNPs were associated with a significant decline in the drug plasma levels accompanied by a lower bleeding risk while maintaining the efficacy in preventing VTE.[20]

Despite the significant contribution to variations in dabigatran troughs and peaks, there was a lack of significant effect of *CES1* SNP (rs8192935) on the risk of developing hemorrhage due to dabigatran.[34]

The metabolic activation of dabigatran was significantly reduced (at 53%) in individuals carrying the variant CES1 G14E in comparison to the WT (at 100%).[37]

Table 4: Dabigatran levels based on genetic polymorphisms of *CES1* and *ABCB1*

Gene	SNP Allelic change	Dabigatran level change (with clinical outcomes findings)
CES1	rs2244613 Intron: C > A	A significant decline in trough levels[34] A significant reduction in hemorrhage risk[34] No significant association with VTE incidents[34] A significant decline in trough levels in allele-carrying individuals[35] No significant association with pharmacokinetics[26] A non-significant decline in trough levels[36]
CES1	rs8192935 Intron: T > C	A significant decline in peak levels[34] No significant association with hemorrhage risk and VTE incidents[34] A significant decline in trough levels in allele-carrying individuals[35]
CES1	rs71647871 536 G > A	A significant decrease in bioactivation of dabigatran[37]
ABCB1	rs1128503 1236 C > T	No significant association with pharmacokinetics[26]
ABCB1	rs2032582 2677 G > T/A	No significant association with pharmacokinetics[26]
ABCB1	rs4148738 intron: A > G	A significant increase in peak levels without a significant effect on hemorrhage risk or VTE incidents[34] No significant association with peak and trough levels[35] A significant increase in peak levels[36] No significant association with pharmacokinetics[22]
ABCB1	rs1045642 (3435 C > T)	The MHM allelic presentation had significantly increased drug peaks and significantly elevated the risk of hemorrhage (Russians)[36]

MHM = mutated homozygous, VTE = venous thromboembolism

ABCB1 gene

The SNPs rs1128503, rs2032582, rs1045642, and rs4148738 were identified as the most frequent SNPs in the *ABCB1* gene.[26]

Sychev *et al.* investigated the effect of SNPs in *ABCB1* and *CES1* genes on dabigatran pharmacokinetics in Russian individuals measured as peak and trough levels. Both dabigatran peaks and hemorrhage risk were significantly greater in the MHM genotype for the SNP 3435 C > T when compared with the WT.[36] The other variants did not significantly affect dabigatran pharmacokinetics.[36]

The SNP rs4148738 in the *ABCB1* gene was estimated to elevate dabigatran maximum concentration by 1.12-fold per minor allele when compared with the WT, but this elevation did not significantly predispose the patients to hemorrhage.[34]

Implementation of genetic screening in clinical practice

Overall, high-quality evidence supporting the screening of the genetic variants of efflux transporter proteins and metabolizing enzymes of anticoagulants is not yet available. Thus, an advisory statement to incorporate genetic analysis to anticoagulation therapy has not been currently endorsed by healthcare organizations.[20]

Furthermore, when the *CES1* rs2244613 and rs8192935 SNPs were searched in the pharmacogenomics database (online database for pharmacogenetics-related research can be accessed by www.pharmgkb.org), the level of evidence was found low (termed as level 3). Similarly, the SNPs of *CYP3A5* rs776746 and *ABCG2* rs2231142 were designated with evidence level 3 for apixaban [see Figure 1 for a summary of DOACs pharmacogenetics and their potential effects].

Lack of sufficient quality research hinders the clinical practice application of pharmacogenetic screening. The inconsistencies in findings and inadequate study designs contribute to the insufficiency of the available evidence.[38]

Interestingly, a promising work (the DAPHNE study, n = 300) is undergoing to investigate the effects of ABCB1 and CYP3A allelic variants, the availability and activity of the drug disposition proteins, and several pharmacokinetic and clinical parameters of rivaroxaban and apixaban. The findings may further elucidate the role of pharmacogenetics in DOAC therapy.[39]

Conclusion

Several SNPs in the genes encoding for the protein sites that interact with the anticoagulant agents have been reported to influence the response to anticoagulant therapy. Interpatient variability and potential adverse events or lack of efficacy could be attributed to such SNPs.

The lack of achieving the therapeutic targets with heparin therapy has been connected to SNPs in the *SERPINC1* gene. In contrast, carriers of the variant allele *HLA-DRB3*01:01* might be predisposed to HIT development.

ABCB1 SNPs were a significant associating factor to higher drug levels in patients receiving anticoagulant therapy with rivaroxaban, apixaban, or dabigatran. SNPs in the gene encoding the metabolizing enzyme (*CYP3A5*)

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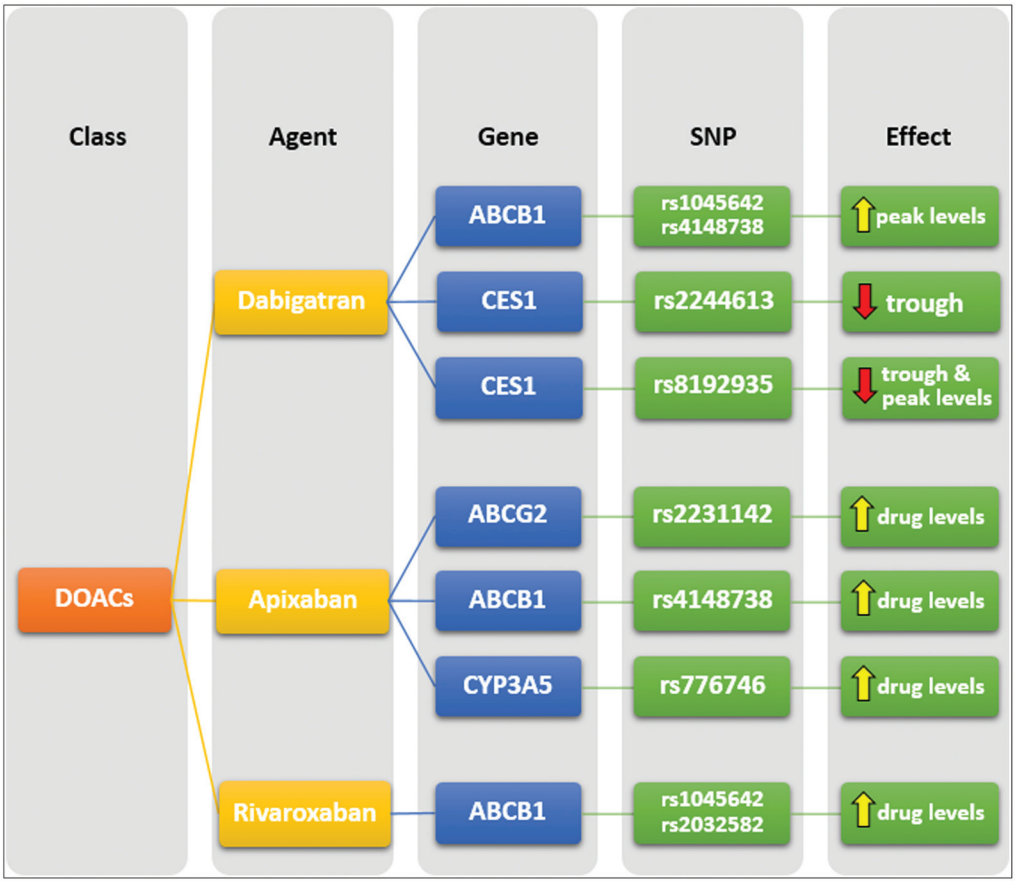

Figure 1: Potential pharmacogenetics of rivaroxaban, apixaban, and dabigatran and associated changes in pharmacokinetics (up-arrows indicate an increase in the concentration level and down arrows indicate a decrease in the concentration level) [Adopted from (24)]

were reported to significantly increase apixaban levels, which could cause bleeding especially if it was concurrent with other bleeding risk factors.

Conversely, the SNP (rs2244613) in the *CES1* gene was associated with significantly lower dabigatran levels in the variant genotypes when compared with the wild-type genotypes, which was reported to protect the variant genotype carriers from bleeding adverse events.

Additional studies are required to investigate other SNPs in the genes encoding for the proteins involved in the anticoagulant pharmacokinetics and pharmacodynamics to identify additional potential contributors to variances in response to anticoagulant therapy. Moreover, more effort is needed to verify whether the documented SNPs have similar effects in different populations.

Authors' contribution

AMAA contributed toward the conception or design of the work, drafting of the work, approval of the final version of the article, and agreed to all aspects of the work. KMA and SKA contributed toward the literature review, revision of the article for important intellectual content, approval of the final version of the article, and agreed to all aspects of the work.

Ethical consideration

Not applicable.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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