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ORIGINAL ARTICLE

Pharmacogenetics of dabigatran and apixaban in association with gastrointestinal bleeding

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Abstract

OBJECTIVES: To determine whether selected single nucleotide polymorphisms (SNPs) of genes encoding proteins responsible for the activation, transport, or metabolism of dabigatran and apixaban might be associated with a risk of gastrointestinal bleeding in a cohort of adult patients treated with these drugs. No previous study has focused specifically on the association with gastrointestinal bleeding.
MATERIALS AND METHODS: Ninety-one patients treated with dabigatran or apixaban were genotyped for selected polymorphisms. The following polymorphisms were studied: *ABCB1* gene rs1045642, rs4148738, rs1128503 and rs2032582; *CES1* gene rs2244613, rs8192935 and rs2244614; and *SULT1A1* gene rs9282861 and *SULT1A2* gene rs1136703. Two groups divided by particular drugs and genotypes were compared in terms of the presence (bleeding group) or absence (nonbleeding group) of gastrointestinal bleeding. The genotype distribution was expressed via dominant and recessive models.
RESULTS: In patients treated either with dabigatran or with apixaban, no evidence was found to support the association of gastrointestinal bleeding with any genotype for any of the studied SNPs.
CONCLUSION: In both dabigatran- and apixaban-treated patients, no associations between the selected polymorphisms and gastrointestinal bleeding risk were found, however the results should be interpreted with caution because of the small cohort size.

Abbreviations:

ABC	- Adenosine triphosphate binding cassette
AF	- Atrial fibrillation
CES	- Carboxylesterase
CI	- Confidence interval
DOACs	- Direct oral anticoagulants
GIB	- Gastrointestinal bleeding
NSAIDs	- Nonsteroidal anti-inflammatory drugs
OR	- Odds ratio
PCR	- Polymerase chain reaction
SNPs	- Single nucleotide polymorphisms
SULT	- Sulfotransferase
VKAs	- Vitamin K antagonists
VTE	- Venous thromboembolism

INTRODUCTION

Dabigatran, rivaroxaban, apixaban and edoxaban are widely used direct oral anticoagulants (DOACs). They directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban). DOACs are the first-line option for the prevention of thromboembolic events in nonvalvular atrial fibrillation (AF) patients and for the treatment and secondary prevention of venous thromboembolism (VTE) (Konstantinides *et al.* 2020; Ortel *et al.* 2020; Hindricks *et al.* 2021). Compared with vitamin K antagonists (VKAs), DOACs have several advantages, such as rapid onset and offset of action, fewer food and drug interactions and fixed-dose administration without the need for routine monitoring (Yeh *et al.* 2015; Navar *et al.* 2022). Although DOACs have been shown to have a favourable safety profile with significantly lower all-cause mortality and intracranial haemorrhage incidence than VKAs does, the risk of bleeding, particularly gastrointestinal bleeding (GIB), is still a concern (Ruff *et al.* 2014; Cheung & Leung 2017). It has been estimated that 0.4–0.7% of patients with AF might experience DOAC-related GIB annually. Age >65 years, hepatorenal dysfunction, low body weight, concomitant prescription of antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs), and drugs that interact with P-glycoprotein or the cytochrome P450 system can increase the risk of GIB (Abraham 2016). There is significant interindividual variability in the therapeutic response, which could be related to polymorphisms in genes encoding proteins responsible for the activation, transport, or metabolism of DOACs, such as *ABCB1*, *CES1*, and *SULT1* (Wang *et al.* 2009; Merali *et al.* 2014; Thompson *et al.* 2023).

All DOACs are P-glycoprotein substrates. The *ABCB1* gene encodes the P-glycoprotein efflux pump, a membrane-associated protein from the superfamily of ATP-binding cassette (ABC) transporters. Single nucleotide polymorphisms (SNPs) of the *ABCB1* gene, rs1045642, rs4148738, rs1128503 and rs2032582, impact the pharmacokinetics of many P-glycoprotein substrate drugs, but the genotype/phenotype relationship of these variants and their connection to the risk of gastrointestinal bleeding is not clear (Gouin-Thibault *et al.* 2017; Sennesael *et al.* 2018; Ueshima *et al.* 2018; Zubiaur *et al.* 2020).

Carboxylesterases are involved in the metabolism and activation of dabigatran. Variations in *CES1*, encoding carboxylesterase 1 (CES1), have been evaluated in relation to dabigatran, apixaban and rivaroxaban. The *CES1* gene SNPs rs2244613 and rs8192935 are associated with pharmacokinetic variations in dabigatran but are not clearly associated with bleeding risk (Paré *et al.* 2013; Merali *et al.* 2014; Sychev *et al.* 2018). The *CES1* gene SNP rs2244614 has not yet been studied in connection with DOACs.

Sulfotransferases are potentially important in the metabolic pathways of apixaban (Wang *et al.* 2009). The gene *SULT1A1* SNP rs9282861 has been shown to be associated with the pharmacokinetics of apixaban (Attelind *et al.* 2022). Its association with the risk of any bleeding is not clear. The effect of *SULT1A2* is less potent than that of *SULT1A1*, and the effect of its SNP rs1136703 on apixaban metabolism has not yet been studied (Wang *et al.* 2009; Shnayder *et al.* 2021).

Nearly all the studied SNPs are known to be involved in either the metabolism or excretion of DOACs (Wang *et al.* 2009; Paré *et al.* 2013; Dimatteo *et al.* 2016b; Sychev *et al.* 2018; Liu *et al.* 2021; Shnayder *et al.* 2021; Ji *et al.* 2021; Attelind *et al.* 2022). However, the associations between genetic variants and the clinical outcomes of DOAC users have been investigated in only a few studies.

The aim of this study was to determine whether selected SNPs might be associated with the risk of gastrointestinal bleeding in a cohort of adult patients treated with dabigatran or apixaban. The following polymorphisms were studied: *ABCB1* gene rs1045642,

Tab. 1. Demographic characteristics of participants

Characteristics	Overall (n=91)	Bleeding group (n=48)	Non-bleeding group (n=43)	*p*-value Bleeding group vs. Non-bleeding group
Age, years, mean (SD)	77.1 (10.2)	78.9 (8.5)	74.5 (11.3)	0.980
Sex, male, n (%)	42 (46.2)	22 (45.9)	20 (46.5)	1.000
Dabigatran, n (%)	45 (49.5)	28 (58.3)	17 (39.5)	0.906
Apixaban, n (%)	46 (50.5)	20 (41.7)	26 (60.5)	0.906

SD, standard deviation

rs4148738, rs1128503 and rs2032582; *CES1* gene rs2244613, rs8192935 and rs2244614; and *SULT1A1* gene rs9282861 and *SULT1A2* gene rs1136703.

MATERIALS AND METHODS

In our monocentric, regional, cross-sectional study, genotyping for selected polymorphisms was performed in 91 patients. All of them were adult Caucasian patients currently treated with dabigatran or apixaban, irrespective of the indication for anticoagulation therapy. All patients lived in the East Bohemian region of the Czech Republic (Central Europe). Data and blood samples were collected at the Emergency Department or at internal departments of the University Hospital, Hradec Kralove.

Two groups divided by particular drugs and genotypes were compared in terms of the presence (bleeding group) or absence (nonbleeding group) of gastrointestinal bleeding. In the nonbleeding group, there was no gastrointestinal bleeding for at least one year from the beginning of DOAC use. The presence of gastrointestinal bleeding was based on the current history or clinical findings of upper gastrointestinal bleeding (haematemesis, melena) or lower gastrointestinal bleeding (enterorrhagia).

Ethics

All participants provided written informed consent before being enrolled in the study, which was approved by the Ethics Committee of the University Hospital, Hradec Kralove, Czech Republic, and was carried out in accordance with the Declaration of Helsinki principles.

Genotyping

Genotyping was performed via real-time PCR with allelic discrimination via commercial TaqMan allele-specific assays (Life Technologies, Grand Island, New York, USA). High-quality data were obtained for all samples and SNPs tested (rs1045642, rs4148738, rs1128503, rs2032582, rs2244613, rs8192935, rs2244614, rs9282861, and rs1136703).

Statistics

The genotype distribution was expressed via a dominant model assuming a dominant effect of the minor allele (less common allele) (mm + mw) versus ww, the wild-type allele (w), the minor allele (m), and a recessive model (mm versus (mw + ww)). The results are expressed as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was considered at a *P* value of 0.05. The Mann-Whitney U-test was used to compare age between groups, while χ^2-test was used

Tab. 2. Baseline clinical charasteristics of patients

	Bleeding group			Non-bleeding group	*p*-value Bleeding group vs. Non-bleeding group
	Dabigatran	Apixaban	Overall	Overall	
Number of patients	28	20	48	43	
DOAC exposure time, months, median (IQR)	9 (2.1 – 21.0)	2.5 (0.5 – 19.0)	5 (1.8 – 20.5)		
Upper gastrointestinal bleeding, n (%)	15 (53.6)	15 (75.0)	30 (62.5)		
Haemodynamic instability, n (%)	11 (39.3)	9 (45.0)	20 (41.7)		
Major comorbidities, n (%)					
Atrial fibrillation	23 (82.1)	16 (80.0)	39 (81.3)	32 (74.4)	0.459
Chronic kidney disease	8 (28.6)	4 (20.0)	12 (25.0)	10 (23.3)	1.000
Coronary artery disease	9 (32.1)	8 (40.0)	17 (35.4)	12 (27.9)	0.504
Diabetes mellitus	7 (25.0)	8 (40.0)	15 (31.3)	13 (30.2)	1.000
Heart failure	7 (25.0)	8 (40.0)	15 (31.3)	10 (23.3)	0.483
Hypertension	24 (85.7)	17 (85.0)	41 (85.4)	33 (76.7)	0.420
Malignancy	5 (17.9)	7 (35.0)	12 (25.0)	12 (27.9)	0.814
Previous stroke or TIA	7 (25.0)	4 (20.0)	11 (22.9)	7 (16.3)	0.599
Venous thromboembolism	6 (21.4)	6 (30.0)	12 (25.0)	14 (32.6)	0.490

DOAC, direct oral anticoagulant; IQR, interquartile range: 25th and 75th percentile; TIA, transient ischemic attack

for frequency data. Statistical analyses were carried out via NCSS Statistical Software 2021, version 21.0.4 (NCSS LLC, Kaysville, Utah, USA).

RESULTS

Data were obtained from 91 patients, with a mean age of 77.1 years and an age range of 36–94 years. In total, 42 (46.2%) patients were men. In the bleeding group, there were a total of 48 patients. (Table 1)

Table 2 shows the clinical characteristics of participants. The median time of DOACs use before gastrointestinal bleeding event was 5 months. There were 30 patients (62,5%) with upper gastrointestinal bleeding. Hemodynamic instability, defined as hypotension (systolic blood pressure < 100mmHg), tachycardia (heart rate > 100/min) or history of syncope, was present in 20 patients (41,7%) in the bleeding group.

In our study, a comparison of dichotomized groups was made with respect to the absence or presence of bleeding. In patients treated with dabigatran, four *ABCB1* gene SNPs were tested (rs4148738, rs1045642, rs2032582, and rs1128503), and three *CES1* gene SNPs were tested (rs8192935, rs2244613, and rs2244614). In all of these SNPs, using recessive and dominant models, we found no evidence to support the association of gastrointestinal bleeding with any genotype. (Table 3)

In patients treated with apixaban, four *ABCB1* gene SNPs (rs4148738, rs1045642, rs2032582, and rs1128503), one *SULT1A1* gene SNP (rs9282861) and one *SULT1A2* SNP (rs1136703) were tested. Not even in these SNPs, using recessive and dominant models, we found no evidence to support the association of gastrointestinal bleeding with any genotype. (Table 4).

DISCUSSION

As mentioned above, nearly all the studied SNPs play a role in the metabolism or excretion of DOACs. While some studies have investigated the links between genetic variants and clinical outcomes for DOAC users, only limited research has been conducted on these specific associations.

To the best of our knowledge, no study has focused specifically on the association with gastrointestinal bleeding.

In our study, we found no association between the *ABCB1* gene SNP rs4148738 and the risk of gastrointestinal bleeding in patients treated with either dabigatran or apixaban. Previous studies on apixaban have reported inconsistent results. Some studies demonstrated an association with lower peak concentrations (Dimatteo *et al.* 2016a), whereas others showed no effect on the pharmacokinetics of apixaban (Kryukov *et al.* 2018). One study reported an association with a reduced risk of bleeding events, in general (Lähteenmäki *et al.* 2021). *ABCB1* gene SNP rs4148738 is known to be associated with higher peak concentrations of dabigatran (Paré *et al.* 2013; Sychev *et al.* 2018), but it is not associated with all bleeding events (Paré *et al.* 2013).

In our study, we did not find any linkage disequilibrium among the *ABCB1* gene SNPs rs1128503, rs2032582, and rs1045642. These SNPs are known for partial linkage disequilibrium (Kim 2001; Kroetz *et al.* 2003). Rivaroxaban-treated patients with the TTT haplotype had a lower thromboembolic risk (Lähteenmäki *et al.* 2021), but there is no known association with pharmacokinetic variability or bleeding risk in dabigatran and apixaban (Gouin-Thibault *et al.* 2017; Nakagawa *et al.* 2021; Yoon *et al.* 2022), which is in agreement with our findings above.

In our cohort, we did not find any association with gastrointestinal bleeding in the *CES1* SNPs studied. Variation in the *CES1* gene has been evaluated mainly in dabigatran users. In dabigatran, the SNP rs2244613 was associated with a lower risk of bleeding, and rs8192935 was associated with neither ischaemic nor bleeding events (Paré *et al.* 2013). There are only a few studies on rs2244614 in DOACs, all without any significant findings (Stangier & Clemens 2009; Xiang *et al.* 2022).

In our study, we found no associations between gastrointestinal bleeding and the *SULT1A1* SNP rs9282861 or the *SULT1A2* SNP rs1136703 in apixaban users. The *SULT1A1* SNP rs9282861 is involved in the metabolism of apixaban; however, no significant associations with pharmacokinetics or bleeding events have been previously published (Kanuri & Kreutz 2019; Attelind *et al.* 2022). The *SULT1A2* SNP rs1136703 has never been studied in DOACs.

Unlike many pharmacogenetic studies on DOACs, which primarily focus on pharmacokinetics, our study emphasizes the risk of gastrointestinal bleeding. Some studies, such as those by Lähteenmäki *et al.* (2021) and Paré *et al.* (2013), have investigated clinical outcomes, though none have specifically addressed the risk of gastrointestinal bleeding in relation to the SNPs we studied. The lack of association between pharmacogenetic factors and the risk of gastrointestinal bleeding could be explained by several factors. Gastrointestinal bleeding risk is influenced by a variety of strong clinical factors, such as age, renal function, and comorbidities (Abraham 2016). These factors may have a more significant impact than genetic variants alone. It is also possible that pharmacogenetic factors might interact with these clinical factors; however, our study's sample size limited the potential for subgroup analyses, such as stratifying by age or presence of renal insufficiency. For the same reason, we were unable to categorize bleeding severity, which might have further influenced the observed associations. Gastrointestinal bleeding can originate from a range of lesions in both the upper and lower gastrointestinal tract (such as ulcers, tumours, diverticula), and assessing pharmacogenetic factors in relation to specific endoscopic findings could provide more detailed insights. As suggested in similar studies, other enzymes and transporters involved in DOAC

Tab. 3. Odds ratio in single nucleotide polymorphisms according to the presence or absence of gastrointestinal bleeding - dabigatran

Genotypes of single nucleotide polymorphisms studied	Bleeding group (n=28)	Non-bleeding group (n=17)	OR (95% CI)	*p*-value
ABCB1 rs4148738				
Recessive model (no wild-type alelle) AA vs. GA + GG				
AA	6	5	0.65 (0.16–2.60)	0.547
GA + GG	22	12		
Dominant model (at least one variant alelle) GA + AA vs. GG				
GG	12	6	1.38 (0.40–4.77)	0.616
GA + AA	16	11		
ABCB1 rs1045642				
CC vs. TC + TT				
CC	10	3	2.59 (0.60–11.24)	0.203
TC + TT	18	14		
TT vs. TC + CC				
TT	7	6	0.61 (0.16–2.27)	0.462
TC + CC	21	11		
ABCB1 rs2032582				
GG vs. TG + TT				
GG	9	6	0.87 (0.24–3.10)	0.828
TG + TT	19	11		
TT vs. TG + GG				
TT	12	6	1.38 (0.40–4.77)	0.616
TG + GG	16	11		
ABCB1 rs1128503				
CC vs. TC + TT				
CC	12	5	1.80 (0.50–6.50)	0.370
TC + TT	16	12		
TT vs. TC + CC				
TT	6	5	0.65 (0.16–2.60)	0.547
TC + CC	22	12		
CES1 rs8192935				
CC vs. TC + TT				
CC	7	3	1.56 (0.34–7.06)	0.567
TC + TT	21	14		

Genotypes of single nucleotide polymorphisms studied	Bleeding group (n=28)	Non-bleeding group (n=17)	OR (95% CI)	*p*-value
TT vs. TC + CC				
TT	10	7	0.79 (0.23–2.73)	0.714
TC + CC	18	10		
CES1 rs2244613				
CC vs. AC + AA				
CC	2	2	2.31 (0.43–12.32)	0.328
AC + AA	26	15		
AA vs. AC + CC				
AA	16	9	1.19 (0.35–3.98)	0.783
AC + CC	12	8		
CES1 rs2244614				
TT vs. CT + CC				
TT	9	6	0.87 (0.24–3.10)	0.828
CT + CC	19	11		
CC vs. CT + TT				
CC	10	4	1.81 (0.46–7.04)	0.395
CT + TT	18	13		

CI, Confidence interval; OR, Odds ratio

metabolism could potentially overshadow the effects of the specific variants studied here (Campos-Staffico *et al.* 2022). While focusing on gastrointestinal bleeding specifically, the main limitation is the small size of the cohort in our single-centre study.

CONCLUSION

In conclusion, nine studied SNPs of four genes were not significantly associated with gastrointestinal bleeding risk in patients treated with dabigatran or apixaban. The results should be interpreted with caution because of the small cohort size and high heterogeneity due to different sources of bleeding (upper or lower gastrointestinal bleeding). Further studies are needed to better understand the role of pharmacogenetics in gastrointestinal bleeding risk in DOAC-treated patients. On the other hand, in current clinical practice, pharmacogenetics is not a key factor in deciding on any anticoagulant therapy. Clinical risk factors and drug interactions must always be considered first.

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Tab. 4. Odds ratio in single nucleotide polymorphisms according to the presence or absence of gastrointestinal bleeding - apixaban

Genotypes of single nucleotide polymorphisms studied	Bleeding group (n=20)	Non-bleeding group (n=26)	OR (95% CI)	*p*-value
ABCB1 rs4148738				
Recessive model (no wild-type alelle) AA vs. GA + GG				
AA	6	7	1.16 (0.32–4.23)	0.818
GA + GG	14	19		
Dominant model (at least one variant alelle) GA + AA vs. GG				
GG	3	9	0.33 (0.08–1.45)	0.143
GA + AA	17	17		
ABCB1 rs1045642				
CC vs. TC + TT				
CC	7	7	1.46 (0.41–5.17)	0.556
TC + TT	13	19		
TT vs. TC + CC				
TT	5	6	1.11 (0.28–4.34)	0.880
TC + CC	15	20		
ABCB1 rs2032582				
GG vs. TG + TT				
GG	4	9	0.47 (0.12–1.84)	0.280
TG + TT	16	17		
TT vs. TG + GG				
TT	6	6	1.43 (0.38–5.36)	0.597
TG + GG	14	20		
ABCB1 rs1128503				
CC vs. TC + TT				
CC	6	6	1.43 (0.38–5.36)	0.597
TC + TT	14	20		
TT vs. TC + CC				
TT	4	9	0.47 (0.12–1.84)	0.280
TC + CC	16	17		
SULT1A1 rs9282861				
AA vs. GA + GG				
AA	2	4	0.61 (0.10–3.73)	0.593
GA + GG	18	22		

Genotypes of single nucleotide polymorphisms studied	Bleeding group (n=20)	Non-bleeding group (n=26)	OR (95% CI)	*p*-value
GG vs. GA + AA				
GG	5	9	0.63 (0.17–2.30)	0.484
GA + AA	15	17		
SULT1A2 rs1136703				
CC vs. TC + TT				
CC	2	4	0.61 (0.10–3.73)	0.593
TC + TT	18	22		
TT vs. TC + CC				
TT	5	8	0.75 (0.20–2.78)	0.667
TC + CC	15	18		

CI, Confidence interval; OR, Odds ratio

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