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REVIEW

Effect of Gene Polymorphism on the Pharmacokinetics and Clinical Outcomes of Rivaroxaban: State-of-the-Art Review

Ling Wang[1,2,*], Guoquan Chen[2,*], Wei Hu[3,*], Jiale Chen[2], Yiling He[1,2]

[1]School of Pharmaceutical Sciences, Zhejiang Chinese Medical University, Hangzhou, People's Republic of China; [2]Department of Pharmacy, Affiliated Jinhua Hospital, Medical College of Zhejiang University, Jinhua, People's Republic of China; [3]Department of Pharmacy, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yiling He, Department of Pharmacy, Affiliated Jinhua Hospital, Medical College of Zhejiang University, Jinhua, People's Republic of China, Email 1538583874@qq.com

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Abstract: Rivaroxaban is a direct oral anticoagulant (DOAC) that directly inhibits coagulation factor Xa and exerts its anticoagulant effects. Although rivaroxaban generally exhibits predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles, significant interindividual variability in therapeutic responses exists. Research on the role of genetic factors in the clinical variability of rivaroxaban is relatively new and extensive. In this review, 12 pharmacogenetic studies on rivaroxaban were summarised, and 25 reported gene polymorphic sites were summarised, including *ABCB1* (rs1045642, rs4148738, rs1128503, rs2032582, rs4728709, rs3789243 and rs3213619, *ABCG2* (rs2231142, rs2231137, rs3114018, rs2622604 and rs1481012), *CYP3A4* (rs35599367, rs2242480, rs4646437 and rs12333983), *CYP3A5* (rs776746, rs15524, rs4646450), *CYP2J2* (rs890293), *CYP2J19* (rs4244285 and rs12248560), *ABCA6* (rs7212506), *AKR7A3* (rs1738023 and rs1738025). The review provided an overview of the current state of research on rivaroxaban gene polymorphisms. However, due to the significant heterogeneity of existing studies and the lack of consistency in results, the evidence to date has limited impact. Therefore, larger-scale, global, multi-centre clinical trials are needed in the future to validate potential gene loci for testing.

Keywords: rivaroxaban, pharmacogenomics, pharmacokinetics, bleeding events, polymorphism, variant

Introduction

Rivaroxaban, the first orally active direct Factor Xa (FXa) inhibitor, is a small-molecule oxazolidinone derivative (a molecular weight of 435.88 Da). It specifically and reversibly binds to the S1 and S4 pockets of FXa with 10,000 times more selectivity than any other related serine proteases, such as thrombin, trypsin, plasmin, Factor VIIa, IXa, XIa, urokinase, or activated protein.[1,2] Rivaroxaban inhibits endogenous FXa activity with an inhibitory concentration 50% (IC_{50}) of 21±1 nM in a concentration-dependent manner[1] and thrombin generation is almost completely suppressed at therapeutic concentrations (80–100 nM).[3]

Based on previous landmark large Phase III randomized clinical trials (RCTs),[4–10] rivaroxaban is recommended for three indications: 1) stroke prevention of atrial fibrillation (AF), 2) reduction of major cardiovascular events in chronic coronary artery or peripheral artery disease, and 3) treatment and secondary prevention of venous thromboembolism (VTE) in adults and pediatric pupulations.[11–14]

Since the approval of the US Food and Drug Administration (FDA) approval in 2011, the prescription volume of rivaroxaban has increased annually and reached 8.6 million in 2020, making it one of the most commonly prescribed medications in the United States.[15] In China, rivaroxaban was approved for clinical use in 2009, and was the most frequently used direct oral anticoagulant (DOACs) in 2017.[16]

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While demonstrating generally predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles, rivaroxaban exhibits substantial interindividual variability in therapeutic responses observed in both healthy populations and patient cohorts. The data from published studies have shown an up to 15-fold variation in rivaroxaban plasma concentration.[17] During phase III trials, rivaroxaban concentrations were associated with clinical outcome, and the interindividual coefficient of variability was approximately 30% to 40%.[18] This variability stems from the interplay between non-genetic factors, particularly renal insufficiency, advanced age, low body weight, and hepatic impairment, with genetic variations affecting drug transporters and metabolic enzymes.

Pharmacogenetics elucidates the genetic determinants of interindividual variability in drug responses, providing a scientific framework for personalized dosing optimization and adverse event mitigation in antithrombotic therapies. Despite robust mechanistic associations between genetic polymorphisms and rivaroxaban PK, clinical translation remains hindered by heterogeneous evidence and insufficient outcome-driven guidelines.

This review synthesizes evidence from 12 studies based on the following inclusion criteria to evaluate genotype-dependent pharmacokinetic variability and bleeding risk stratification: 1) patients undergoing treatment with rivaroxaban who are of any race, sex or age; 2) reported at least one of the different SNPs on kinetic parameters for subjects or a certain clinical outcome. The exclusion criteria were duplicate publications, literature published in languages other than English, abstracts without essential details and unqualified data. The main characteristics of the included studies are summarized in Tables 1 and 2.

Pharmacokinetic and Pharmacodynamic Profile

Rivaroxaban exhibits high oral bioavailability (80–100%) with dose-dependent food effects; administration with food enhances the bioavailability of the 15/20 mg doses to >80%, while the 10 mg dose remains unaffected. Peak plasma concentrations (C_{max}) were achieved within 2–4 h of dosing. The drug was highly protein-bound (92–95%, primarily albumin), resulting in a moderate volume of distribution (~50 L).

The elimination of rivaroxaban proceeds via a dual pathway, including the metabolic degradation of the drug and renal elimination of the unchanged drug, see Figure 1. Approximately two-thirds of ingested rivaroxaban is subjected to metabolic degradation by cytochrome P450 enzymes (CYP3A4/5:50% of the total metabolism; CYP2J2:14%) and non-CYP-mediated mechanisms. No pharmacologically active metabolites were detected in the plasma. Renal elimination accounts for one-third of the dose, comprising glomerular filtration (passive) and active tubular secretion mediated by efflux transporter P-glycoprotein (P-gp, encoded by *ABCB1*) and breast cancer resistance protein (BCRP, encoded by *ABCG2*).

Pharmacogenetic

The Effects of ABCB1 Polymorphisms

The humans *ABCB1* gene[31] is adjacently located on chromosome 7q21, encoding a drug transporter (P-gp).[32] A total of 12 studies investigated *ABCB1* genetic variants, with predominant focus on four clinically relevant loci: rs1045642 (n=12 studies), rs4148738 (n=9), rs1128503 (n=8) and rs2032582 (n=7). Secondary loci (rs4728709, rs3789243 and rs3213619) were examined in a single study. There was substantial methodological heterogeneity across the studies, including statistical approaches, bleeding outcome definitions, and pharmacokinetic measurement protocols.

Regarding the types of site mutations, the reported studies did not use a uniform notation system. Therefore, in subsequent descriptions, the same site mutation may be represented in two different ways (Table S1). For example, the site rs1045642 is denoted as c.3435T>C when using the cDNA sequence as a reference and as g.87138645A>G when using the genomic sequence as a reference. However, this does not affect the interpretation of the study results.

rs1045642 (g.87138645A>G)

Among the 12 studies investigating rs1045642 in this review, two yielded discordant ethnicity-specific findings. In Asian populations, heterozygous (AG) and homozygous (GG) mutant genotypes correlated with reductions in rivaroxaban peak plasma concentrations (C_{max}) compared to wild-type (AA) carriers ($P<0.05$),[19] whereas no such association was observed

Table 1 Main Characteristics of the Included Studies

Study ID	Country	Ethnicity	Diagnosis	No. of patients	Male/ Female	Age,Mean (SD) Median [range]	Rivaroxaban Dose (mg)	Dietary Condition (fed/fasted)
Ain N U et al (2024)[19]	Pakistan	Asian	NVAF	66	NR	NR	10mg,15mg,20mg qd	NR
Lenoir C et al (2022)[20]	Switzerland	Caucasian	AF, VTE	135	89/46	71.1 (12.1)	10, 15, 20 mg qd 15 mg bid	NR
NakagawaJ et al (2021)[21]	Japan	Asian	AF	86	73/13	62.4 (10.6)	10, 15 mg qd	Fed
Wang Y et al (2021)[22]	China	Asian	AF	155	81/74	71.98(10.72)	15, 20 mg qd	NR
Sychev D et al (2022)[23]	Russia	Caucasian	AF	128	NR	87.5[83.0–90.0]	15, 20 mg qd	NR
Sychev D A et al (2022)[24]	Russia	Caucasian	AF	86	42/44	67.24 (1.01)	20 mg qd	NR
Wu T et al (2023)[25]	China	Asian	NVAF	95	56/39	65.8 (12.5)	10,15,20 mg qd	NR
Sennesael A L et al (2018)[26]	Belgium	Caucasian	AF,VTE	10	2/8	NR	15 mg,20 mg	NR
Kim H et al (2023)[27]	Korea	Asian	AF,VTE	92	NR	NR	NR	NR
Campos-Staffico A M et al (2022)[28]	USA	Non-Hispanic /Hispanicor /Latino	NVAF	2634	1606/758	68.3(13.6)	19±3.5 mg daily dose	NR
Zhang D et al (2022)[29]	China	Asian	AF	216	102/114	NR	2.5–20 mg qd	NR
Sychev D A et al (2020)[30]	Russia	Caucasian	NVAF	103	56/47	73(9.8)	NR	NR

Abbreviations: SD, standard deviation; NVAF, non-valvular atrial fibrillation; AF, atrial fibrillation; VTE, venous thromboembolism; NR, not reported; qd, once daily; bid, twice daily.

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Table 2 Visual Representation of Investigated SNP and Outcomes in Each Study

Study ID	*ABCB1*	*ABCG2*	*CYP3A4*	*CYP3A5*	*CYP2J2*	*CYP2C19*	HWE	Hemorrhage	Pharmacokinetic Outcomes
Ain N U et al (2024)[19]	rs1045642 rs1128503 rs2032582 rs4148738	NR	NR	rs776746	NR	NR	Yes	√	C_{max}
Lenoir C et al (2022)[20]	rs1045642 rs1128503 rs2032582	NR	NR	NR	NR	NR	Yes	NR	$AUC_{0\text{-}6h}$;C_{2h}
NakagawaJ et al (2021) [21]	rs1045642 rs2032582 rs1128503	rs2231142	NR	rs776746	rs890293	NR	Yes	NR	C_{0h};C_{0h} /D
Wang Y et al (2021)[22]	rs1045642 rs1128503 rs4148738	NR	NR	NR	NR	NR	Yes	√	C_{0h}
Sychev D et al (2022)[23]	rs1045642 rs4148738	NR	NR	NR	NR	NR	Yes	√	C_{trough}
Sychev D A et al (2022)[24]	rs1045642 rs4148738	NR	rs35599367	rs776746	NR	NR	Yes	NR	C_{trough}
Wu T et al (2023)[25]	rs1045642 rs1128503 rs4148738 rs4728709	rs2231137 rs2231142	rs2242480 rs4646437	rs776746	NR	NR	Yes	√	C_{trough}/D
Sennesael A L et al (2018)[26]	rs1128503 rs2032582 rs1045642 rs4148738	NR	NR	NR	NR	NR	Yes	NR	C_{trough}
Kim H et al (2023)[27]	rs1045642 rs2032582 rs1128503 rs3789243 rs3213619	rs2231142 rs2231137 rs2622604 rs3114018 rs1481012	rs2242480 rs4646437 rs12333983	rs776746 rs15524 rs4646450	NR	NR	Yes	√	NR
Campos-Staffico A M et al (2022)[28]	rs1128503 rs2032582 rs1045642 rs4148738	rs22131142	rs35599367	rs776746	rs890293	NR	Yes	√	NR
Zhang D et al (2022) [29]	rs1045642 rs4148738 rs2032582	NR	NR	rs776746	rs890293	rs4244285 rs12248560	Yes	√	C_{max}/D
[30] Sychev D A et al (2020)	rs1045642 rs4148738	NR	NR	rs776746	NR	rs4244285 rs12248560	Yes	√	C_{trough}

Abbreviations: HWE, Hardy–Weinberg equilibrium; NR, not reported; √ indicates the outcomes were reported; AUC, area under the curve; C_{2h}, concentration 2 h after drug administration; C_{0h} or C_{trough}, trough concentration; C_{0h} or C_{trough}/D, plasma trough concentration/dose; C_{max}, peak concentration; C_{max}/D, plasma peak concentration/dose.

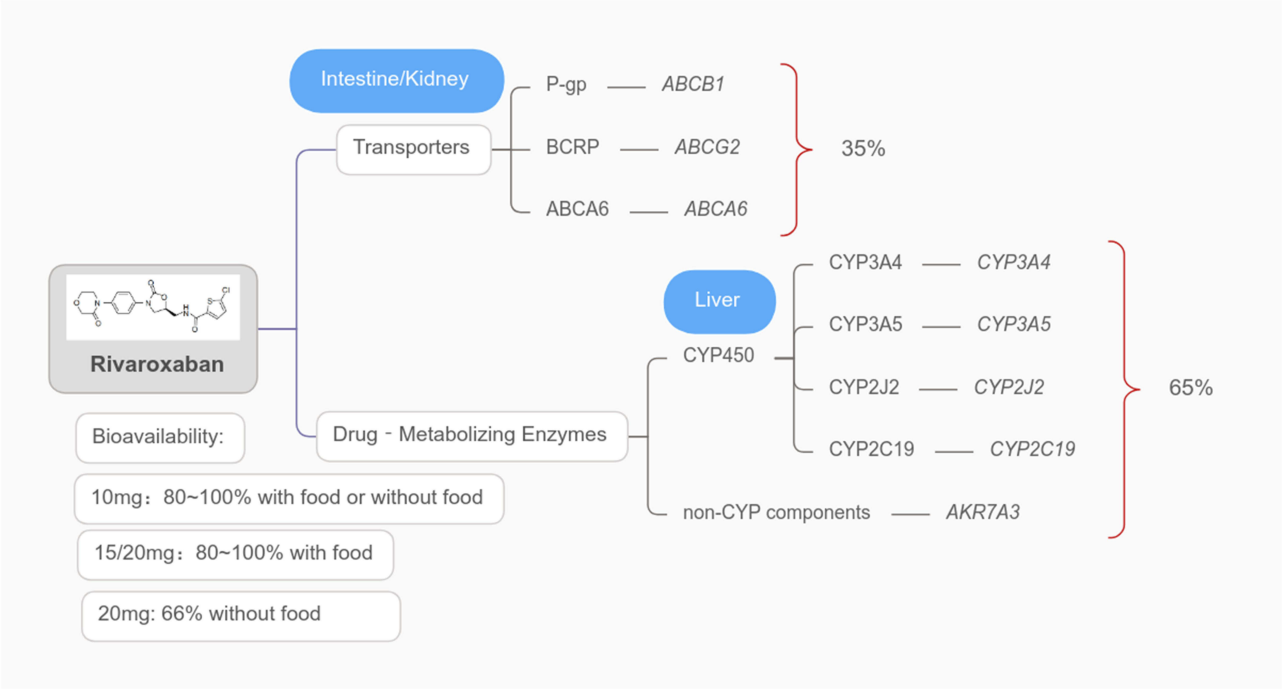

Figure 1 Proteins and genes associated with the transport and metabolism of rivaroxaban.
Notes: *ABCB1, CYP3A4* and other italics in the figure and text refer to genes encoding related proteins.*ABCB1* loci include rs1045642 (n=12 studies), rs4148738 (n=9), rs1128503 (n=8) and rs2032582 (n=7),rs4728709, rs3789243, rs3213619 (n=1); *ABCG2* loci include rs2231142 (n=4), rs2231137 (n=2), rs3114018 (n=1), rs2622604 (n=1), rs1481012 (n=1); *ABCA6* locus include rs7212506 (n=1); *CYP3A4* loci include rs35599367 (n=2), rs2242480 (n=2), rs4646437 (n=2), rs12333983 (n=1); *CYP3A5* locus include rs776746 (n=7), rs15524 (n=1), rs4646450 (n=1); *CYP2J2* locus include rs890293 (n=3); *CYP2C19* loci include rs4244285 (n=2),rs12248560 (n=2); *AKR7A3* loci include rs1738023 (n=1),rs1738025 (n=1).
Abbreviations: P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; CYP450, Cytochrome P450.

in Caucasian cohorts (heterozygous for mutation, β=−8.53, CI: (−32.11, 15.04); homozygous for mutation, β=−12.17, CI: (−32.48 to 8.14).[20] This discrepancy likely reflects ethnic disparities in both allele frequencies and baseline drug exposure profiles. Data from the NCBI database's global population study shows that the gene frequency distribution in European and American populations is A=0.521607, G=0.478393, while in East Asian populations, the gene frequency distribution is A=0.3838, G=0.6162. Meanwhile, research shows that Japanese populations exhibit a 20–40% higher rivaroxaban area under the curve (AUC) than Caucasians.[33] Despite these C_{max} variations, five studies consistently reported null associations between rs1045642 and trough concentration (C_{min}) or dose-adjusted residuals across diverse populations (P>0.10).[21–25]

Bleeding risk correlations remain contentious owing to the methodological heterogeneity. Sennesael et al[26] first identified a non-significant trend toward bleeding in variant allele carriers, although this was limited by a small cohort (n=10). Subsequent studies have reported contradictory findings. Sychev et al[23] reported an increased risk of clinically relevant non-major bleeding (CRNMB) in TT versus CC genotypes (29.3% vs 4.5%, P= 0.021), while Kim et al[27] demonstrated a confounder-adjusted elevated major bleeding risk in AA genotype carriers (Model I: 3.243 (1.371–-7.671); Model II: 3.167 (1.349–7.436). Conversely, Wang et al[22] observed no association among Mongolian descendants (P=0.9107), which potentially reflects ancestry-specific penetrance. Other studies have also failed to observe any correlation.[28,29]

Critical limitations include inconsistent outcome definitions, variable adjustments for renal function and P-gp inhibitors, and population stratification effects. These unresolved discrepancies underscore the necessity for standardized phenotyping protocols and ancestry-stratified analyses in future pharmacogenomic investigations.

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rs4148738 (g.87163049C>T)

The *ABCB1* rs4148738 polymorphism exhibited conflicting pharmacogenetic associations across nine observational studies. Five studies found no significant correlation between the rs4148738 genotypes and C_{min} in either Asian or Caucasian cohorts.[19,22,23,26,30] However, subsequent studies revealed population-specific effects: Sychev et al demonstrated that Caucasian patients with the CT genotype had higher residual drug concentrations than CC wild-type carriers (P = 0.039),[24] while Wu Tingting et al observed that Asian TT homozygotes showed lower dose-adjusted C_{min} (C_{min}/D) compared to CC genotypes [median (IQR) TT: 0.66 (0.31,1.20) vs CC: 1.22 (0.66,3.47); Adjusted P = 0.033][25] It reported that no correlation was observed between peak concentration and this locus.[29]

Regarding bleeding events, one study[23] reported that the *ABCB1* rs4148738 mutant genotype (CT/TT) was associated with an increased incidence of bleeding events compared to the wild-type genotype (CC) (TT vs CC 39.3% vs 8.1%, P = 0.008; TT vs CT 39.3% vs 14.3%, P = 0.002), which is supported by other studies[19,28] In contrast, efficacy assessments focusing on anticoagulation intensity demonstrated no significant alterations in PT levels across the rs4148738 genotypes (P=0.640488).

rs1128503 (g.87179601A>G)

This systematic review incorporated eight studies investigating the *ABCB1* rs1128503 polymorphism. Wang et al demonstrated that Mongolian ethnic carriers of the wild-type genotype exhibited a significantly higher C_{min} than those with mutant genotypes [TT: 33.80 (19.00, 51.90) vs CC: 29.10 (15.61, 57.22), P=0.0421].[22] Ain N U et al reported that the heterozygous and homozygous mutant showed lower peak concentrations as compared to the wild-type genotype [AA: 12.06±7.31; AG: 6.51 ±4.15; GG: 5.66±2.42].[19] However, subsequent investigations in multi-ethnic cohorts, including Asian populations[21,25] and European/American populations,[20] failed to establish statistically significant associations between this genetic variant and pharmacokinetic parameters.

Notably, while Wang et al identified genotype-dependent concentration variations, no direct genetic correlation with bleeding events was observed (P=0.8062),[22] suggesting potential synergistic effects of other pharmacogenetic factors or clinical variables on hemorrhagic outcomes. These findings were corroborated by independent studies by Wu et al,[25–28] which collectively demonstrated the absence of significant genotype-bleeding associations.

Other Loci

Wu et al first identified a clinically significant association between the *ABCB1* rs4728709 polymorphism and C_{min}/D, with heterozygous GA genotype carriers demonstrating significantly reduced C_{min}/D values compared to wild-type GG individuals (GA vs GG, P = 0.032) [median (IQR): GA: 0.40 (0.30,0.88) vs GG: 1.06 (0.50,1.81); Adjusted P = 0.032].[25] This seminal finding provides novel insights into the genetic determinants of rivaroxaban pharmacokinetic variability of rivaroxaban. Notably, complementary evidence from dexamethasone studies revealed that the rs4728709 variant accelerates drug clearance of this P-gp substrate,[34] resulting in corresponding reductions in systemic exposure, a mechanistic parallel consistent with Wu's pharmacometric observations.

Divergent observations regarding *ABCB1* rs2032582 exist in the current literature. Zhang et al reported an elevated dose-adjusted C_{max} (C_{max}/D) in G allele carriers (P = 0.025, FDR = 0.042)[29] and Ain N U et al reported mutant genotypes showed lower peak concentrations as compared to the wild-type genotype,[19] whereas Lenoir C et al found no significant influence of this polymorphism on C_{max}[20] and Nakagawa et al found no significant influence of this polymorphism on C_{min}/D,[21] necessitating further validation in larger pharmacogenetic cohorts.[26] Meanwhile, no correlation was found in the studies of bleeding events related to this locus.[27,28] Exploratory analyses of less-characterized variants (rs3789243 and rs3213619) have thus far failed to establish significant associations with either rivaroxaban pharmacokinetic parameters or hemorrhagic outcomes (P=0.346; P=0.696).[27]

In summary, the correlation between *ABCB1* polymorphisms and rivaroxaban pharmacokinetics and hemorrhagic events has not been harmonized, and there are considerable differences among different ethnic groups. Most of the available data are from Caucasians, and very little data are available for the Chinese population. Therefore, further research is needed to explore the correlation between *ABCB1* gene polymorphisms and P-gp

expression, especially in multi-tissue, multi-site, pharmacokinetics and pharmacodynamics, a more systematic study should be carried out on the Chinese population, and further research on the effects of *ABCB1* gene polymorphisms and P- gp expression and functional differences on drug disposal, so as to provide a theoretical and practical basis for clinical rational drug use.

The Effects of ABCG2 Polymorphisms

ABCG2 encodes BCRP, an ATP-binding cassette efflux transporter that mediates the cellular extrusion of various substrates including rivaroxaban.[6] BCRP is predominantly expressed on the apical membrane of intestinal epithelial cells, where it modulates drug bioavailability by actively transporting substrates from the enterocytes into the intestinal lumen. The transporter is also functionally expressed in critical pharmacological barriers and excretory organs, including the blood-brain barrier (limiting central nervous system penetration of substrates), hepatocytes (facilitating hepatobiliary elimination), and renal proximal tubules (mediating active secretion into urine).

Our systematic review included four pharmacogenetic studies that investigated clinically relevant *ABCG2* polymorphisms: rs2231142 (n=4), rs2231137 (n=2), rs3114018 (n=1), rs2622604 (n=1), and rs1481012 (n=1).

Regarding the pharmacokinetic outcomes, we have not identified any *ABCG2* gene polymorphisms associated with the pharmacokinetics of rivaroxaban. Although *ABCG2* rs2231137 and rs2231142 are missense mutations, four studies consistently demonstrated that these loci are not associated with the pharmacokinetic parameters (C_{trough}/D) of rivaroxaban.[21,25,27,28] Regarding bleeding events, the finding that A carriers of rs3114018 were associated with bleeding complications was supported by Kim (A allele carriers 26.8% vs CC genotype carriers 15.6%, P=0.020).[27] Although the SNP is located in an intron non-expressed region, it is possible that those located in the control region of the *ABCG2* gene, both in intron and promoter sequences, could affect RNA splicing and thus interfere with the expression/function of *ABCG2* proteins, or could result in modified substrate selectivity.[35] Kim et al found no significant ABCG2 variants (rs2622604/rs1481012) beyond rs3114018.[27] As ABCB1 (P-gp) and ABCG2 (BCRP) exhibit overlapping substrate specificity and synergistic effects, further clinical studies are required to clarify their combined effects on rivaroxaban pharmacokinetic, efficacy and bleeding risk.[32]

The Effects of CYP3A4/5 Polymorphisms

Genetic polymorphisms in cytochrome P450 (CYP) enzymes, particularly the CYP3A4/5 isoforms, have been implicated in interindividual variability in drug metabolism.[36] Similarly, studies have also demonstrated a strong correlation between CYP3A family activity and rivaroxaban metabolism.[37] Therefore, it stands to reason that genetic polymorphisms in the CYP3A family would be associated with the clinical outcomes of rivaroxaban. However, the results of many recent studies contradict this assumption. This review analyzed seven studies that investigated *CYP3A4/5* variants (rs35599367, rs2242480, rs4646437, rs12333983 in *CYP3A4* and 3* rs776746, rs15524, rs4646450 in *CYP3A5*).

No significant associations were observed between *CYP3A5* 3* (rs776746) and rivaroxaban exposure[21,24,30] or between *CYP3A4* (rs35599367) and C_{min} in atrial fibrillation patients, which aligns with previous research findings.[21,24,25,30] Wu et al also did not find that *CYP3A4* gene polymorphisms (rs2242480 and rs4646437) had a significant effect on the C_{min}/D of rivaroxaban. No correlation was observed between *CYP3A4/5* (including the above sites and rs12333983, rs15524, rs4646450) and hemorrhage events.[25,27–29] The current data do not support definitive correlations between CYP3A4/5 genetic variants and the PK or efficacy of rivaroxaban.

The Effects of CYP2J2 Polymorphisms

CYP2J2 accounts for approximately 14% of the total clearance of rivaroxaban, which is comparable to the contribution of CYP3A.[38] Notably, the catalytic efficiency of CYP2J2 is higher than that of CYP3A4 in vitro. The intrinsic clearance of rivaroxaban catalyzed by CYP2J2 is nearly 39 times greater than that catalyzed by CYP3A4.[39] Among the three studies that analyzed *CYP2J2* genetic variants in this review, all focused exclusively on the *7 allele (rs890293).

It was noted that there was no correlation between *CYP2J2**7 (rs890293) and C_{min}/D (P=0.331) or C_{max}/D (P=0.445) in two studies,[21,29] in terms of safety, Zhang et al and Campos et al also did not observe a significant association between *CYP2J2**7 (rs890293) and bleeding events (P=0.999).[28,29] CYP2J2 activity is affected by various polymorphisms (such as *CYP2J2**2, *3, *4, *6, *8, and *10).[39] While current evidence remains inconclusive regarding *CYP2J2*-mediated pharmacodynamic interactions with rivaroxaban, the polymorphic landscape of the gene warrants further investigation to elucidate the potential subpopulation-specific effects obscured by phenotypic heterogeneity.

The Effects of CYP2C19 Polymorphisms

Although CYP2C19 contributes to rivaroxaban metabolism, pharmacogenomic analyses of two key polymorphisms (*CYP2C19**2 [rs4244285] and *17 [rs12248560]) revealed no significant pharmacokinetic associations. A study of patients with atrial fibrillation and acute coronary syndrome demonstrated that neither *CYP2C19* *2 nor *17 polymorphism significantly influenced the C_{min} of rivaroxaban.[30] Complementary findings from a separate investigation showed that the *CYP2C19* *17 variant was not associated with multiple pharmacokinetic parameters (C_{min}, C_{min}/D, C_{max}/D) and bleeding outcomes.[29]

Notably, current evidence does not support the clinically relevant *CYP450* genetic determinants of rivaroxaban pharmacokinetics. This apparent paradox, in which CYP450 enzymes mediate metabolic clearance yet lacks identified genetic modifiers, may reflect methodological limitations in existing studies. Key constraints include underpowered sample sizes, heterogeneous patient populations, and insufficient characterization of rare *CYP450* variants. Systematic pharmacogenomic investigations employing standardized pharmacokinetic phenotyping and multi-ethnic cohorts are required to resolve potential population-specific effects and to elucidate the complex interplay between genetic variation and rivaroxaban metabolism.

Other Genes

The metabolism of rivaroxaban is mainly dependent on the CYP subtypes described above as well as on non-CYP components. AKR7A3 is a member of the AKR family and is involved in exogenous drug metabolism. Considering the complexity of rivaroxaban metabolism, there is a study based on whole-exome sequencing to explore candidate genes associated with the potential bleeding risk of rivaroxaban. Zhao et al found that compared with heterozygous variants and unmutated genotypes, homozygous *ABCA6* rs7212506 and *AKR7A3* rs1738023/rs1738025 were susceptible sites for bleeding events with rivaroxaban.[40] ABCA6 is a member of the ATP-binding cassette transporter superfamily that transports both extracellular and intracellular substrates, including drugs and metabolites. They predicted that the *AKR7A3* homozygous variant could block the normal metabolism of rivaroxaban, causing systemic accumulation of the active parent drug, while speculating that the *ABCA6* homozygous variant might disrupt transmembrane stability and perturb the ABC transporter signaling pathway, thereby altering the disposition of rivaroxaban.

A study[41] exploring the genetic background of DOACs-associated hemorrhagic events found that specific haplotypes (eg, AAAGAGCT and AGAG) were significantly more frequent in hemorrhagic patients than in controls (P<0.05), although no significant differences in any of the examined single-nucleotide variants (SNVs) were detected in hemorrhagic patients. This suggests that haplotype analysis can reveal genetic markers significantly associated with DOACs-related adverse events (AEs) that may not be detected in individual SNV analyses.

Summary

This systematic review synthesizes current evidence on the pharmacokinetic profile of rivaroxaban (encompassing absorption, distribution, metabolism, and excretion characteristics) and pharmacogenetic determinants. Through a critical appraisal of methodological approaches and clinical implications across the included studies, we characterized population-specific variations in drug disposition and evaluated putative genetic biomarkers. Our analysis established an evidence-based framework to (1) identify knowledge gaps in CYP450-mediated metabolic pathways and transporter interactions, (2) quantify the clinical validity of reported genotype-phenotype

associations, and (3) assess the evidentiary threshold for implementing genetic testing to optimize rivaroxaban dosing strategies.

Known factors that increase the risk of bleeding during rivaroxaban treatment include renal and hepatic impairments, concomitant therapy with interacting drugs, low body weight, and advanced age.[42] While pharmacogenetic profiling holds the theoretical potential to guide personalized anticoagulant selection by minimizing interindividual variability in drug exposure, thereby balancing thromboembolic prevention against bleeding risk, current evidence remains insufficient to establish clinically actionable genotype-phenotype correlations. The 25 genetic loci included in the 12 genetic polymorphism studies in this paper include well-known, extensively studied loci as well as newly discovered loci reported in individual studies that are associated with individual differences in rivaroxaban. However, as mentioned earlier, when studying ABCB1 rs1045642, previous reports have shown that the correlation with Cmax varies across different ethnic groups. While many studies have not observed any association with Cmin. First, the data are derived from studies with different statistical methods, results, definitions, and measurements, which may lead to inconsistencies in the results. However, inconsistencies do not mean that such studies are meaningless; they merely highlight the complexity and extremity of clinical data, further emphasising the importance of real-world validation.

In summary, pharmacogenomic monitoring and bleeding risk assessment prior to rivaroxaban administration may help optimise its efficacy and safety in patients. However, whether clinically actionable genotype-phenotype correlations can be established requires larger-scale, robust, global, multicentre clinical trials to validate the potential genetic loci identified by the test and a large-scale data repository to provide the foundation for personalised treatment.

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Disclosure

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