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An Investigation of the Correlation Between the ABCB1 Rs4728709 Gene Polymorphism with Rivaroxaban Response and Bleeding Events in Patients with Atrial Fibrillation from Tthe Southern Region of Iraq

Haider Khudhair Jalel[1,2] *, Mazin Ouda Hamid[1]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Iraq

[2] Department of Pharmacy, Thi Qar Health Directorate, Ministry of Health, Iraq

***Corresponding Author**

Haider Khudhair Jalel: haiderkhudhair96@gmail.com

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Abstract

Background: Atrial fibrillation (AF) is a frequently occurring heart rhythm disorder that causes substantial morbidity and mortality due to thromboembolic events. Rivaroxaban, a direct oral anticoagulant (DOAC), is often prescribed to prevent strokes in patients with non-valvular AF. However, the impact of genetic variables on the pharmacokinetics and clinical effects of rivaroxaban in patients with non-valvular atrial fibrillation (NVAF) in Iraq still insufficiently explored.

Aim of Study: This study explores the link between the single-nucleotide polymorphism (SNP) in the ABCB1 gene (rs4728709 G>A), rivaroxaban response, and the occurrence of bleeding events in patients with atrial fibrillation (AF).

Patients and Methods: This cross-sectional study examines patients with atrial fibrillation (AF) treated with rivaroxaban anticoagulation from September 2024 to March 2025 in Iraq. We gathered clinical data covering demographics, comorbidities, and treatment adherence. Biochemical tests assessed coagulation parameters (INR, PT) and complete blood count (CBC) for (HB, PLT). Genotyping for the ABCB1 SNP was conducted using allele-specific polymerase chain reaction (AS-PCR).

Results: This study included 100 participants, comprising 45 males and 55 females, predominantly over 46, and exhibited a high obesity rate of 52%. The genotype distribution for rs4728709 was 72% GG, 13% GA, and 15% AA. The rs4728709 polymorphism was not significantly associated with rivaroxaban response and occurrences of bleeding events.

Conclusion: The rs4728709 polymorphism in the ABCB1 gene showed no significant association with rivaroxaban response or bleeding events among Iraqi patients with non-valvular atrial fibrillation, indicating limited pharmacogenomic relevance of this SNP in anticoagulation response within the studied population.

التحقق من العلاقة بين تعدد الأشكال الجيني ABCB1 rs4728709 واستجابة عقار ريفاروكسابان وحدوث نزيف لدى مرضى الرجفان الأذيني في جنوب العراق.

حيدر خضير جليل ومازن عوده حامد

الخلاصة

الخلفية: يُعرف الرجفان الأذيني (AF) بانه اضطرابًا شائعًا في نظم القلب، ويتسبب في معدلات عالية من المراضة والوفيات نتيجة للانسدادات التخثرية. يُستخدم عقار ريفاروكسابان، وهو مضاد تخثر فموي مباشر (DOAC)، بشكل شائع للوقاية من السكتات الدماغية لدى المرضى الذين يعانون من الرجفان الأذيني غير الصمامي (NVAF). ومع ذلك، فإن تأثير العوامل الوراثية في الحركية الدوائية والتأثيرات السريرية لعقار ريفاروكسابان لدى المرضى العراقيين المصابين بالرجفان الأذيني غير الصمامي لا يزال غير مستكشَف بشكل كافٍ.

أهادف الدراسة: هدفت هذه الدراسة إلى استكشاف العلاقة بين تعدد الأشكال الجيني (SNP) في جين ABCB1 (rs4728709 G>A)، واستجابة عقار ريفاروكسابان، وحدوث حالات النزيف لدى المرضى المصابين بالرجفان الأذيني (AF).

المرضى والطرق: اجريت هذه الدراسة المقطعية على مرضى يعانون من الرجفان الأذيني (AF) ويتلقون علاج ريفاروكسابان المضاد للتخثر في العراق خلال الفترة من سبتمبر 2024 إلى مارس 2025. تم جمع بيانات سريرية شملت الخصائص الديموغرافية، الأمراض المصاحبة، والالتزام بالعلاج. كما تم إجراء اختبارات بيوكيميائية لتقييم معايير التخثر (INR، PT) وفحص تعداد الدم الكامل (CBC) بما في ذلك (HB، PLT). وتم تحديد النمط الجيني لتعدد الأشكال الجيني ABCB1 باستخدام تقنية تفاعل البوليميراز المتسلسل الخاص بالأليل (AS-PCR).

النتائج: شملت الدراسة 100 مشارك، منهم 45 ذكور و55 إناث، وكانت الغالبية تزيد أعمارهم عن 46 عامًا، مع معدل سمنة مرتفع بلغ 52%. كان توزيع الأنماط الجينية لتعدد الأشكال rs4728709 كالتالي: 72% GG، 13% GA، و15% AA. ولم يكن هناك ارتباط ذو دلالة إحصائية بين تعدد الأشكال rs4728709 واستجابة عقار ريفاروكسابان أو حدوث حالات النزيف.

الاستنتاج: لم يُظهر تعدد الأشكال rs4728709 في جين ABCB1 ارتباطًا ذا دلالة إحصائية مع استجابة عقار ريفاروكسابان أو حدوث حالات النزيف بين المرضى العراقيين المصابين بالرجفان الأذيني غير الصمامي. تشير هذه النتائج إلى محدودية الأهمية الصيدلانية الجينية لهذا التعدد الجيني في استجابة العلاج المضاد للتخثر ضمن السكان الذين شملتهم الدراسة.

1. Introduction

Atrial fibrillation (AF) is the predominant form of supraventricular arrhythmias, affecting approximately 1% of the worldwide community. Its frequency significantly rises with age, potentially affecting about 10% of older adults. (Linz et al., 2024). It is very common, about 1 in 3 to 5 individuals over 45 face a lifetime risk. From 2010 to 2019, The worldwide incidence of atrial fibrillation increased dramatically from 33.5 million - 59 million affected people. (Vinciguerra et al., 2024). Etiology or disease persistence can be used to classify this condition. When AF is categorized by persistence, it can be separated into four forms. The first type is called paroxysmal AF, and it resolves either on itself or with intervention within seven days of beginning. of onset. The second type is Persistent AF, which continues for over a period of seven days, includes episode which are terminated by cardioversion (whether it's pharmacological nor electrical) following a total of seven days. The third type is Long-standing Persistent AF, characterized as Continuous AF lasting exceeding twelve months if a rhythmic control approach is employed. Finally, Permanent AF will be recognized by both the individual and doctor, indicating no additional steps to recover or sustain sinus rhythm are planned. (Kirchhof et al., 2016). The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) illustrates the data estimated global population affected by AF reached 55.4 million in 2022. (Mensah et al., 2023). Atrial fibrillation demonstrates a growing prevalence and incidence as age increases, (Schnabel et al., 2015) that's the main cause of risk for myocardial infarction (MI), heart failure (HF), tobacco use, alcohol consumption, body weight index, elevated blood pressure, hypertrophy of the left ventricle, and sex. (Kornej et al., 2020; J. Zhang et al., 2021). Preventing stroke has consistently been essential in the treatment of this condition. Most guidelines favor for non-VKA oral anticoagulants, also known as direct oral anticoagulants, owing to their superior safety, effectiveness, and convenience compared to Vitamin K antagonists, leading to an increasing utilization in healthcare settings. (Hohnloser et al., 2019). The development of direct oral anticoagulants (DOACs), exemplified by rivaroxaban, represents a significant advancement in medicine. (Chen et al., 2020). Rivaroxaban, the first oral direct inhibitor of factor Xa (FXa), has been approved for both the prevention and treatment of DVT (deep vein thrombosis) and PE (pulmonary embolism), in addition to reducing the possibility of stroke and embolism in atrial fibrillation non-valvular.(Schwarb & Tsakiris, 2016). Despite the lack of routine coagulation monitoring for DOACs, the incidence of severe bleeding episodes has occasionally been documented in individuals using these medications. Rivaroxaban ranked among the top ten pharmaceuticals linked to emergency department visits due to adverse medication events in the United States during 2013-2014. (Shehab et al., 2016). In addition, the interindividual variation in the pharmacokinetics of rivaroxaban among individuals with non-valvular atrial fibrillation (NVAF) has been shown to be considerably large (Hori et al., 2012; Xu et al., 2012). According to in vitro and in vivo drug interaction studies, the P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) are the carriers linked to the active renal secretion of rivaroxaban.(Gnoth et al., 2011). Genetic variations among individuals in drug-metabolizing enzymes and transporters affect the effectiveness and safety of various medications. Pharmacogenomics, a crucial component of precision medicine, examines individual responses to medications based on genomic information, facilitating the assessment with particular genetic variations that influence drug response (Ahmed et al., 2016). The ABCB1 gene, or multidrug resistance 1 (MDR1), encodes P-glycoprotein (P-gp), which is present on the surface of epithelial cells. It inhibits intestinal absorption, protects the fetus and brain from xenobiotic exposure, and promotes

renal and hepatobiliary excretion. P-glycoprotein is expressed in a polarized fashion within the plasma membrane of cells in barrier and excretory organs, serving protective and eliminatory roles. It significantly contributes to first-pass clearance of orally ingested medications, thereby restricting their bioavailability by effluxing pharmaceuticals of the lumen-exposed epithelia in the small intestine as well colon, in addition to from the bile-exposed canaliculi in the liver. It removes substrates that reside in systemic circulation via the urine-facing portion of the brush border membrane in the proximal tubule of the kidneys and subsequently through biliary excretion (Hodges et al., 2011). Numerous genetic variations that could potentially influence the efficacy of rivaroxaban therapy in vivo have been proposed. For the first time, one previous study identified that the ABCB1 rs4728709 gene polymorphism substantially influenced the C_{trough}/D of rivaroxaban in individuals with atrial fibrillation. Ninety-five individuals participated in this study and 9 gene loci were analyzed. The dose-adjusted trough concentration ratio (C_{trough}/D) of rivaroxaban was significantly lower in the homozygous mutant type compared to the wild type at the ABCB1 rs4148738 locus, and the mutant type also exhibited a significantly lower ratio than the wild type at the ABCB1 rs4728709 locus. (Wu et al., 2023). The use of DOACs has increased significantly in Iraq over the past two years. Nevertheless, there is a lack of studies examining their pharmacogenomics. Thus, this study aims to investigate how gene polymorphism rs4728709 ABCB1 affects response of rivaroxaban and bleeding incidents. The findings may offer insights for the appropriate clinical application of rivaroxaban and encourage the way for further research into the genetic factors influencing its pharmacokinetics and clinical outcomes.

2. Material, Patients and Method

2.1. Study Design

This observational cross-sectional study took place in Thi-Qar province between early September 2024 and March 2025, focusing on the evaluation of rs4728709 SNP in individuals with Atrial Fibrillation. The study included one hundred Iraqi patients diagnosed with nonvalvular atrial fibrillation who had commenced anticoagulant therapy. All participants were prescribed rivaroxaban 20mg once daily for a minimum of six months. We gathered clinical data such as sex, height, weight, coagulation parameters (INR, PT), and complete blood count (CBC) for (HB, PLT). We documented any bleeding events after the medication was initiated. The main inclusion criteria were: 1) participants older than 18 years; 2) confirmed diagnosis of nonvalvular AF with a need for anticoagulation therapy (excluding those with artificial heart valves and significant mitral stenosis), with diagnoses made by attending physicians based on clinical symptoms and electrocardiogram results; 3) capable and willing for providing informed consent. We excluded patients with a confirmed diagnosis of valvular AF (including those with artificial heart valves and significant mitral stenosis), those at high risk of bleeding, individuals having suffered a stroke within the past month, a history of hemorrhagic strokes, recognized non-cardiovascular diseases linked to unfavorable prognosis, hepatic diseases related to coagulopathy, swallowing difficulties, and those concurrently taking DOACs or drug groups like CYP3A4 and P-gp inhibitors (such as amiodarone, verapamil, diltiazem, quinidine, ticagrelor, and clarithromycin) or CYP3A4 and P-gp inducers (including rifampicin, carbamazepine, phenobarbital, phenytoin, pantoprazole, and atenolol). Patients with a history of hypersensitivity or contraindications to rivaroxaban, pregnant or breastfeeding individuals, and any known contraindications to study-related procedures were also excluded. Ultimately, we enrolled 100 patients with AF: 45 men and 55 women.

2.2. Genotyping of The Single Nucleotide Polymorphisms

The current study focuses on the ABCB1 gene (rs4728709). Following DNA extraction, allele-specific Polymerase Chain Reactions (AS-PCR) were performed. After that, PCR products were run across a gel electrophoresis enabled via a UV-trans illuminator.

2.3. Primers

The primers were created by Professor Dr. Hassan Mahmood utilizing Primer Blast software (http: www.ncbi.nih.gov/tools/primer-blast) and sent to Macrogen for additional manufacture. The forward and reverse primers' sequences and product sizes are listed in Table1.

Table 1: Primer Sequence of ABCB1 Gene rs4728709 G> A

Primer set tubes	Nucleotide sequence	Product length
rs4728709	5- ATTTAGCCCATCTGAGTCCAG-3	
Reverse G allele	5- ATTTAGCCCATCTGAGTCCAA-3	
Reverse A allele		
Forward common	5- ACAGTGCCTGAAACACCCTA -3	275

2.4. Optimization of Polymerase Chain Reaction (PCR) Conditions

The desired conditions for ABCB1 (rs4728709) can be achieved using:

1. 3µl of DNA sample
2. 1.5µL of sense primer
3. 1.5µL of antisense primer
4. 12.5µL PCR master mix
5. 6.5µL of nuclease-free water

Table2: Optimized PCR Program for rs4728709

Step	Temperature/ °C	Time in seconds	Cycles number
Initial denaturation	95	5 minutes	1
denaturation	95	25 seconds	35
Annealing	59	30 seconds	
Extension	72	1 minute	
Final extension	72	7 minutes	1

2.5. Statistical Analysis

The collected data of the present study were entered from patients' sheets and analyzed through the Statistical Package for the Social Sciences (IBM SPSS version 26). The data were presented as frequencies and percentages or mean and standard deviation in appropriate tables and graphs. ANOVA test with post hoc analysis was used where is appropriate to find out the possible association between the related variables of the current study for normal distributed data. Furthermore, Kruskal Wallis test was executed with Bonferroni correction for non-normal distributed data and the data presented as median (IQR). Besides, correlation test was done to detect association between some variable under the study. Statistical association was considered significant when p value equal or less than 0.05 (P value ≤ 0.05).

3. Results

A total of 100 patients were enrolled, comprising 45 males and 55 females. Each patient was administered rivaroxaban at a dose of 20 mg once daily. The demographic characteristics of these patients are detailed in Table3. Results regarding the distribution of the ABCB1 genotype can be found in Table4. Notably, the allele frequency distribution of this gene shows a deviation from the Hardy–Weinberg equilibrium, Table5 and Fig.1.

Table3: Descriptive Statistics of The Demographic Characteristics of The Studied Patients, (N=100)

Variable		N	Percent
Sex	Male	45	45
	Female	55	55
Age	30-45	9	9
	46-60	42	42
	>60	49	49
BMI	Underweight	0	0
	Normal	13	13
	Over weight	35	35
	Obese	52	52
Compliance	Good	89	89
	Fair	1	1
	Bad	10	10
Diabetes mellitus	Yes	36	36
	No	64	64
Hypertension	Yes	85	85
	No	15	15
Bleeding event	Yes	9	9
	No	91	91

Table4: Distribution of Gene Polymorphism for SNP rs4728709 Genotype In Patients(N=100)

The Variable		The Frequency	Percent
Genotype SNP rs4728709	GG wild	72	72
	GA hetero	13	13
	AA homo	15	15

Table5: Hardy–Weinberg Equilibrium for, SNP (rs4728709) in Patients

Variable			Frequency	Percent	Alleles		Hardy–Weinberg equilibrium X^2 test
Genotype	GG wild	Observed expected	72 61.62	72% 61.62%	G	A	
	GA hetero	Observed expected	13 33.76	13% 33.76%	157 78.5%	43 21.5%	**X^2 = 37.8067 P<0.001 (S)**
	AA homo	Observed expected	15 4.62	15% 4.62%			

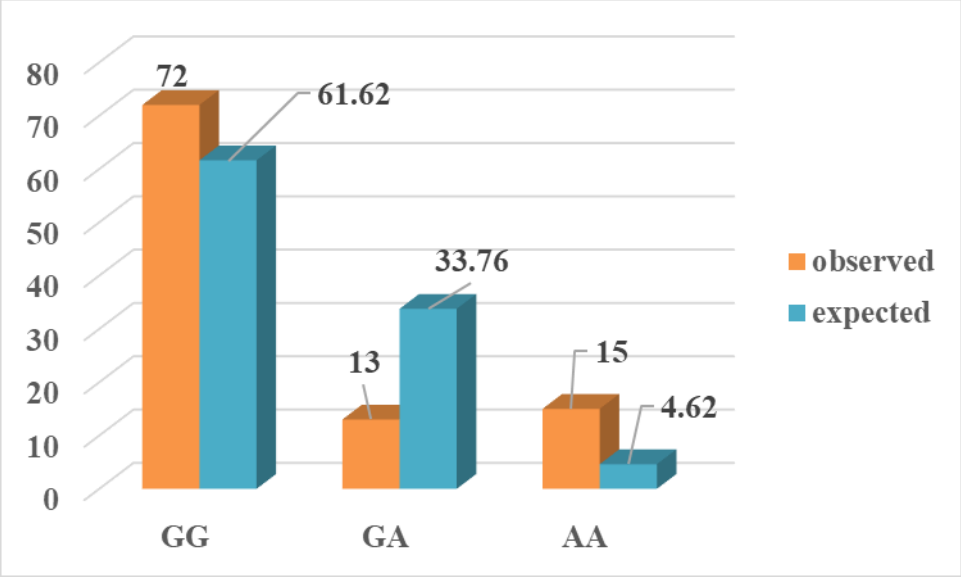

Figure1: Hardy–Weinberg equilibrium analysis of SNP rs4728709. comparison between **observed and expected genotype frequencies** (GG, GA, and AA) for the **rs4728709** single nucleotide polymorphism among the study population. The observed genotype counts were **72 (GG)**, **13 (GA)**, and **15 (AA)**, while the expected frequencies under Hardy–Weinberg equilibrium were **61.62 (GG)**, **33.76 (GA)**, and **4.62 (AA)**. The differences between observed and expected values indicate deviation from Hardy–Weinberg equilibrium in the studied population.

As shown in Table6, there was no significant association (p value <0.05) exists between coagulation parameters and the various genotypes of the ABCB1 G>A (rs4728709) polymorphism. Kruskal-Wallis test had been used with a significant p value <0.05 Results are described as median with IQR. ANOVA test had been used with a significance p value < 0.05 Results are described as mean ± SD. We addressed the hemorrhagic events in the enrolled participants. Out of 100 patients, 9 experienced such events, with no fatal hemorrhages reported. The most frequent types of bleeding included epistaxis and gum bleeding. We examined potential correlations between hemorrhagic incidents and polymorphisms in the ABCB1 gene. No significant association was found between variants at the rs4728709 locus and the incidence of bleeding events ($p > 0.05$). The findings are detailed in Table7.

Table6: Association of Coagulation Parameters and Concentration Level with Different Genotype of ABCB1Gene G>A (rs4728709) Polymorphism in Patients

Parameter	GG	GA	AA	P value
INR	1.20 (0.25)	1.30 (0.15)	1.15 (0.31)	0.417
PT	13.65 (2.37)	14.40 (1.90)	13.10 (3.37)	0.690
PLT	211.00 (78)	226.00 (136)	213.00 (59)	0.742
S.Cr.	0.900 (0.3)	0.800 (0.3)	0.800 (0.3)	0.472
Parameter	GG	GA	AA	P value
Hb	13.11±1.57	12.72±1.78	12.78±1.38	0.584
B.U.	37.29±10.36	39.77±7.5	40.37±10.40	0.400

Table7: Association of genetic variation and bleeding events

SNP	Genotype	Bleeding	No-bleeding	P value
rs4728709	GG	7	65	0.337
	GA	2	11	
	AA	0	15	

A Spearman correlation analysis investigated the relationships among demographic and biochemical parameters showed in Table8. The INR and PT demonstrate a significant positive correlation ($p = 0.833$, $P < 0.001$) as described in the Table 8, indicating that elevated INR values are closely linked to prolonged PT, which reflects coagulation dynamics. Serum creatinine exhibits a strong correlation with blood urea ($p = 0.554$, $P < 0.001$), indicating a dependence of renal function on these two markers. Hemoglobin (HB) exhibits a negative correlation with age ($p= -0.203$, $P= 0.043$) as well BMI ($p= -0.212$, $P= 0.034$), indicating that older individuals and those with elevated BMI may have reduced hemoglobin levels.

Table8: Pearson Correlation Analysis Among Demographic, Hematological, Coagulation, And Renal Parameter

Parameters	Age	BMI	INR	PT	PLT	S.Cr.	HB	B. UREA
Age	1.000	-.183	.068	.109	-.052	-.013	-.203*	.142
BMI	-.183	1.000	.030	-.009	.019	-.110	-.212*	-.056
INR	.068	.030	1.000	.833**	-.040	.092	.028	.036
PT	.109	-.009	.833**	1.000	-.028	.143	.062	.163
PLT	-.052	.019	-.040	-.028	1.000	-.248*	-.105	-.210*
S.Cr.	-.013	-.110	.092	.143	-.248*	1.000	.250*	.554**
HB	-.203*	-.212*	.028	.062	-.105	.250*	1.000	.055
B. UREA	.142	-.056	.036	.163	-.210*	.554**	.055	1.000

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

4. Discussion

This study delineates the socio-demographic characteristics of the patient, analysis of coagulation parameters, and conducts a molecular examination of one SNP in the ABCB1 gene. The aim is to investigate the influence of ABCB1 genetic variations on the response of rivaroxaban and the incidence events of bleeding in individuals with non-valvular atrial fibrillation. Alongside new data pertinent to the pharmacogenetic study of this medication in Iraq. Interindividual variability in response to the medication rivaroxaban may be partly attributed to gene variations encoding the transporter p-gp (Kanuri & Kreutz, 2019). Nevertheless, information about the impact of genetic variants on pharmacological responses remains controversial. Consequently, this cross-sectional study illustrates the association between genetic variants and rivaroxaban response, highlighting the importance for future genetic analysis for rivaroxaban. The ABCB1 gene rs4728709 (G > A) was amplified using polymerase chain reaction (PCR). The results demonstrated that the G allele was the predominant allele, while the A allele was the recessive allele in the population we studied, resembling the findings observed in the Chinese population (F. Zhang et al., 2022). Distributions of genotypes are deviated from Hardy–Weinberg equilibrium, indicating potential biological or population-level factors influence on this locus. Regarding the efficacy (response) outcomes, the assessment of coagulation indicators INR and PT across various genotypes for the SNP rs4728709 shows no statistically significant changes among the patients examined. Yi Ma and his colleagues presented similar findings on efficacy outcomes, including PT and INR levels; no significant correlation was observed between ABCB1 rs4148738, rs4728709, and PT levels across different studies (Ma et al., 2024). This study is the first to assess how various genetic variations influence the response of rivaroxaban and bleeding incidents in patients with NVAF in Iraq. Our results indicate that variations in the P-glycoprotein produced by the ABCB1 gene may influence the response of rivaroxaban. In vitro studies suggest that several SNPs in the ABCB1 gene may correlate with P-gp expression and function alterations (Hodges et al., 2011). The findings highlight the

functional consequences of the ABCB1 rs4728709 polymorphism, likely through the modulation of gene expression, transporter efficacy, by reduced mRNA stability or altered splicing efficiency, potentially resulting in reduced P-glycoprotein levels. In these situations, diminished drug efflux may result in elevated intracellular accumulation. No significant correlation was found between ABCB1 gene polymorphism and bleeding events. However, we recognize the limited sample size of our study, and further research with larger sample sizes is needed to validate the associations between gene polymorphisms and bleeding events. The usage of DOACs has grown in frequency over the past two years in Iraq. However, their associated Pharmacogenomic studies are limited, and larger Population studies are essential to investigate the significance of genes in anticoagulants treatment. Pharmacogenomics for individuals promises to offer precise and logical guidance for patients undergoing anticoagulant therapy.

5. Conclusion

The rs4728709 SNP of the ABCB1 gene studied in Iraqi atrial fibrillation patients did not significantly influence the response to rivaroxaban. No significant correlation was found between the rs4728709 locus and bleeding events. The relationship between genetic variants and bleeding occurrences necessitates confirmation through a larger sample size.

6. Ethical Approval

The study protocol received approval from the research and ethical committee at the University of Karbala's College of Pharmacy. Before proceeding, most physician in the Nasiriyah Heart Center were consulted. Each patient was requested to obtain permission after being informed about the purpose and nature of the study.

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