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Original Article

Comparative Risk of Gastrointestinal Major Bleeding with Rivaroxaban and Warfarin

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Abstract

Background: Warfarin has been the primary anticoagulant medication for a long period. However, its efficacy presents clinical challenges, particularly due to the increased risk of bleeding. The introduction of NOACs, such as rivaroxaban, has revolutionized anticoagulation therapy. Nevertheless, evidence regarding their potential side effects has been conflicting. This study aimed to compare the incidence of major bleeding between rivaroxaban and warfarin.

Methods: This cohort study was conducted at Ghaem Hospital's emergency department, involving patients admitted between December 2019 and September 2021 for any reasons. To qualify, the participants were required to have a recorded history of taking warfarin or rivaroxaban for at least one year. The data on major bleeding incidents within the first year of medication usage were collected and then the outcomes were compared between rivaroxaban and warfarin users.

Results: A cohort of 402 patients were enrolled in this study, with 203 patients on warfarin and 199 on rivaroxaban. During a one-year follow-up, there were four cases of bleeding in the rivaroxaban group and six in the warfarin group. Upper gastrointestinal bleeding occurred in four patients taking warfarin and one patient taking rivaroxaban, while lower gastrointestinal bleeding was reported in two warfarin users and three rivaroxaban users. Despite these differences, they were not statistically significant (p=0.370), and no patient experienced cerebral hemorrhage.

Conclusion: Recommending rivaroxaban might help lower complications and offer a safer treatment option for patients with a history of atrial fibrillation, pulmonary embolism, deep vein thrombosis, or ischemic cerebrovascular accident.

Keywords: Gastrointestinal hemorrhage, Rivaroxaban, Warfarin

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Introduction

Warfarin has been widely established as the gold-standard oral anticoagulant for both prevention and treatment of stroke and thromboembolism in patients with Atrial Fibrillation (AF) and Venous Thromboembolism (VTE), including Deep Vein Thrombosis (DVT), and Pulmonary Embolism (PE) (1,2). As a Vitamin K antagonist, warfarin indirectly inhibits coagulation factors (II, VII, IX, X) and proteins C and S, impacting their synthesis in the liver (2,3). However, despite its effectiveness in preventing venous thrombosis, the use of warfarin poses several important clinical challenges (4). These include a narrow therapeutic index, frequent dose adjustments, potential interactions with other drugs and foods, and, most importantly, a high risk of bleeding (5). Bleeding incidents often lead to discontinuation of anticoagulant therapy, leaving patients at increased risk of thromboembolism (5). Consequently, determining the appropriate warfarin dosage with best therapeutic effect requires careful monitoring of prothrombin time, expressed as the International Normalized Ratio (INR) (6,7).

In recent years, there has been a remarkable shift in the prescription patterns of anticoagulants by physicians. This change can be attributed to the introduction of Non-vitamin K Oral Anticoagulants (NOACs) and the favorable results observed in phase 3 trials. These trials have investigated the effectiveness and adverse effects of NOACs in patients with or at risk of conditions like ischemic stroke, systemic embolism, and Non-Valvular Atrial Fibrillation (NVAF), in comparison to the previously used Vitamin k Antagonists (VKAs) (8-10). NOACs have revolutionized anticoagulant therapy by simplifying the treatment process. Unlike VKAs, they eliminate the need for initial parenteral injection and continuous laboratory monitoring. Moreover, NOACs have fewer drug-drug and drug-food interactions, a wider therapeutic window, and a faster onset of action (1,5). This is because NOACs specifically target a single factor in the coagulation cascade, which differentiates their mechanism of action from that of warfarin (11).

Despite the growing use and benefits of NOACs, studies have reported conflicting results regarding their side effects, particularly bleeding. Multiple clinical trials comparing edoxaban, rivaroxaban, dabigatran, and apixaban with warfarin, revealed a lower risk of intracranial hemorrhage associated with all four medications. However, the risk of gastrointestinal bleeding was found to be higher in edoxaban, rivaroxaban, and dabigatran, with only apixaban demonstrating a lower risk of gastrointestinal bleeding (8-10,12). Dabigatran, when administered at a daily dose 150 *mg*, showed a significantly higher risk of gastrointestinal bleeding, and an increased need for transfusion was reported with the use of rivaroxaban (8,9). Furthermore, a retrospective cohort study involving 46163 patients indicated no significant difference in adjusted hazard ratios between dabigatran and warfarin, as well as between rivaroxaban and warfarin. However, the adjusted hazard ratio of dabigatran compared to rivaroxaban appeared to be significant, suggesting a higher risk of gastrointestinal bleeding associated with dabigatran (13).

Rivaroxaban is a NOAC that functions as a direct factor Xa inhibitor and has been approved by FDA. The dosing of rivaroxaban varies depending on the indication and the risk of bleeding. A prophylactic dose of 10 *mg* daily is commonly used, while a therapeutic dose of 15 *mg* twice daily for three weeks, followed by 20 *mg* daily, is considered appropriate (14).

Despite the numerous benefits of rivaroxaban over warfarin, the occurrence of gastrointestinal major bleeding following the use of this medication remains a concern. Taking into account the conflicting outcomes from different studies and the substantial importance of the risk of bleeding in patients receiving anticoagulants, further investigations are required. To the best of our knowledge, no comparative clinical follow-up studies comparing the VKAs and NOACs have been conducted in Iran. Therefore, the primary objective of this study was to investigate and compare the incidence of major hemorrhagic events associated with rivaroxaban and warfarin during the first year of drug initiation through a cohort study.

Materials and Methods

The present study consisted of a retrospective and prospective cohort study enrolling patients who had initiated anticoagulant therapy with either rivaroxaban or warfarin one year prior to their hospital admission. The study was conducted in Ghaem Hospital, from December 2019 to September 2021, and was granted

ethical approval by the Ethics Committee of Mashhad University of Medical Sciences, assigned with the reference number IR.MUMS.Medical.REC.1398.366. All the patients who met the following criteria were included: diagnosis of AF heart rhythm, a history of pulmonary embolism, DVT or ischemic CVA; no prior gastrointestinal bleeding or hemorrhagic CVA before initiating treatment with rivaroxaban and warfarin; no renal failure as determined by GFR<15 *ml/min*; absence of moderate or severe liver failure, and no presence of cardiovascular disease with heart valve replacement. However, patients who met any of the following exclusion criteria were not included in the study: refusal to participate in the one-year follow-up assessment, administration of other anticoagulant medication during the one-year follow-up period, unavailability to complete file information or incomplete medical records, occurrence of gastrointestinal bleeding or hemorrhagic CVA before commencing treatment with rivaroxaban and warfarin, presence of moderate-to-severe liver failure, and presence of cardiovascular disease with heart valve replacement.

Comprehensive data on demographic details, laboratory studies, and information on the concurrent use of antiplatelet agents or NSAIDs were systematically collected and documented for each patient using an appropriate checklist. Data was also gathered on any history of major bleeding incidents within the first year of drug initiation, as well as the duration of rivaroxaban and warfarin usage. In this study, GI bleeding as a complication of anticoagulation therapy was defined as any type of GI bleedings including hematemesis, melena, and rectorrhagia. In the presents study, the primary objective was to explore and compare the risk of GI bleeding and major hemorrhagic events in patients utilizing rivaroxaban *vs*. warfarin. Furthermore, various factors including the demographic details, medication usage, and clinical events, were also considered to provide valuable insights into the field of anticoagulation therapy.

Statistical analysis

The patients' data were entered and analyzed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Continues variables were expressed as mean ± standard deviation (SD). The categorical variables presented as n (%). The normality of data distribution was tested using the Kolmogorov-Smirnov test. To compare the frequency of the qualitative variables between warfarin and rivaroxaban groups, either the Chi-square or Fisher's exact tests were applied. Additionally, independent t-test was utilized to compare normally and non-normally distributed quantitative variables, respectively. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 402 patients who received either rivaroxaban or warfarin were enrolled in this study to assess the incidence of major bleeding within the first year of drug usage. Among them, 203 patients were administrated warfarin while 199 patients received rivaroxaban. The demographic and primary clinical characteristics of the patients are presented in table 1. The mean age of all the participants was 61.2±14.2 years, ranging from 19 to 90 years old. Upon analyzing the data based on the prescribed medication, the average age was found to be 62.6±13.3 years for warfarin users and 59.8±14.9 years for rivaroxaban group. In terms of gender distribution, 98 (48.3%) patients in the warfarin group and 104 (52.3%) patients in the rivaroxaban group were male. According to the Chi-square test, no significant difference was observed for gender distribution between the two groups (p=0.424). Regarding the drug dosage, among patients utilizing warfarin, 56.2% received a daily dosage of 5 *mg*, while 38.4% received 2.5 *mg* per day. As for patients taking rivaroxaban, the majority (56.8%) were prescribed a daily dosage of 10 *mg*, and 23.6% took 5 *mg* per day. The mean duration of drug usage for warfarin and rivaroxaban was measured as 2.2±1.8 years and 2.4±1.6 years, respectively with no significant difference (p=0.322). Although the majority of demographic and clinical characteristics were comparable between the two groups, a statistically significant difference in age was noted (p=0.047).

GI Bleeding Events

Regarding the primary outcome of major bleeding, the findings of this study revealed that out of 203 patients receiving warfarin treatment, upper GI

Table 1. Distribution of the demographic characteristics and drug-related variables of the patients in the two groups of warfarin and rivaroxaban users

Characteristics		Rivaroxaban N=199	Warfarin N=203	p-value
Age(year)*		14.9±59.8	13.3±62.6	0.047
Gender**	Male	104(52.3)	98(48.3)	0.424
	Female	95(47.7)	105(51.7)	
Duration of use(year)*		2.4±1.6	1.8±2.2	0.322
Dosage**	2.5 *mg*	6(3.0)	78(38.4)	<0.001
	5.0 *mg*	47(23.6)	114(56.2)	
	10.0 *mg*	113(56.8)	7(3.4)	
	15.0 *mg*	6(3.0)	3(1.5)	
	≥20.0 *mg*	27(13.6)	1(0.5)	

*T-Test was used. **Chi-Square Test was used.

Table 2. Distribution of bleeding frequency during one year of using warfarin and rivaroxaban based on gender and age

Characteristics		Bleeding Types	Rivaroxaban N=199	Warfarin N=203	p-value*
GI Bleeding		GIB Upper	1(0.5)	4(2.0)	0.370
		GIB Lower	3(1.5)	2(1.0)	
Gender	Male	GIB Upper	0	3(3.0)	0.179
		GIB Lower	1(1.0)	1(1.0)	
		Cerebrovascular	0	0	
		No bleeding	103(99.0)	94(95.9)	
	Female	GIB Upper	1(1.1)	1(1.0)	0.802
		GIB Lower	2(2.1)	1(1.0)	
		Cerebrovascular	0	0	
		No bleeding	92(96.8)	103(98.1)	
Age(yr)	≤40	GIB Upper	1(3.6)	0	0.99<
		GIB Lower	1(3.6)	1(5.3)	
		Cerebrovascular	0	0	
		No bleeding	26(92.9)	18(94.7)	
	41-60	GIB Upper	0	0	0.486
		GIB Lower	1(1.9)	0	
		Cerebrovascular	0	0	
		No bleeding	53(98.1)	140(98.0)	
	61≤	GIB Upper	0	4(3.1)	0.123
		GIB Lower	1(0.9)	1(3.1)	
		Cerebrovascular	0	0	
		No bleeding	116(199)	122(96.1)	

GI: Gastrointestinal

*Fisher Exact test was used.

Table 3. Distribution of the frequency of bleeding during one year of using warfarin and rivaroxaban based on the use of antiplatelet drugs

Anti-Platelet Medication		Bleeding in the first year	Rivaroxaban N=199	Warfarin N=203	p-value*
Aspirin	+	GIB Upper	0	2(3.3)	0.768
		GIB Lower	1(2.6)	1(1.7)	
		Cerebrovascular	0	0	
		No bleeding	38(97.4)	57(95.0)	
	-	GIB Upper	(0.6) 1	2(1.4)	0.843
		GIB Lower	(1.3) 2	1(0.7)	
		Cerebrovascular	0	0	
		No bleeding	157(98.1)	140(98)	
Plavix	+	GIB Upper	0	0	0.333
		GIB Lower	1(50.0)	0	
		Cerebrovascular	0	0	
		No bleeding	1(50.0)	4(100.0)	
	-	GIB Upper	1(0.5)	4(2.0)	0.449
		GIB Lower	2(1.0)	2(1.0)	
		Cerebrovascular	0	0	
		No bleeding	194(98.5)	193(97.0)	

GI: Gastrointestinal bleeding

*Fisher Exact test was used.

bleeding occurred in four patients, while two patients experienced lower GI bleeding within the first year of drug administration. In the group of rivaroxaban users, one patient experienced upper GI bleeding, and three patients experienced lower GI bleeding. None of the patients exhibited cerebral hemorrhage. The statistical analysis indicated no significant difference in the occurrence of major bleeding between two groups in the first year of drug usage (p=0.370) (Table 2). Additionally, when performing stratified analysis based on the gender and age groups, no significant differences were observed in the incidence of GI bleeding (p=0.179 for gender and p=0.802 for age group) (Table 2).

According to the data on anti-platelet medications, it was found that 29.6% of the patients using warfarin and 19.6% of those using rivaroxaban were also taking aspirin. The consumption of aspirin was significantly higher in the warfarin group (30%) compared to the rivaroxaban group (20%) (p=0.02). Additionally, approximately 2.0% of the patients in warfarin group and 1.0% of those in rivaroxaban group were taking clopidogrel as an anti-platelet medication simultaneously. However, there was no significant difference between the two groups regarding the use of clopidogrel (p=0.685). Furthermore, when conducting a stratified analysis considering the use of anti-platelet drugs, no significant differences were found in the incidence of GI bleeding between the warfarin and rivaroxaban groups (p>0.05) (Table 3).

Risk of bleeding complications

Data regarding the overall bleeding profile of the patients throughout the entire duration of treatment

were also analyzed. The results revealed that bleeding complications, including hematemesis, melena, and rectorrhagia, were observed in 70.9% of the patients who received warfarin, while only 3.0% of the patient's receiving rivaroxaban had at least one type of bleeding complications. These results demonstrated a significantly higher risk of bleeding complications in patients receiving warfarin ($p<0.001$). This is a significant finding, as it highlights the potential risks associated with warfarin therapy. Patients receiving warfarin should be closely monitored for signs of bleeding complications, and prophylactic measures should be considered to reduce the risk of bleeding.

Discussion

In this cohort study, a significantly higher rate of bleeding complications was observed in patients taking warfarin compared to those taking rivaroxaban. Within the first year of drug use, warfarin group experienced 4 cases of upper GI bleeding and 2 cases of lower GI bleeding. However, these occurrences led to no statistically significant difference in major bleeding events when compared to the rivaroxaban group ($p=0.370$). Neither group experienced cerebral hemorrhage in the first year of drug consumption. Despite a higher consumption of aspirin among the warfarin users, the simultaneous use of these two drugs resulted in no increased incidence of bleeding events compared to rivaroxaban. Additionally, no gender or age-related differences in the incidence of GI bleeding were observed between the two study groups.

In line with the current study, the results of the XALIA and EINSTEIN DVT investigations were in favor of rivaroxaban therapy (15,16). XALIA was a multicenter, international, prospective, non-interventional study conducted in 21 countries, involving 4009 patients with DVT. The study showed a lower frequency of major bleeding and recurrent venous thromboembolic events in patients using rivaroxaban. Similarly, the EINSTEIN DVT study, which included 3449 patients with acute DVT, yielded the same outcomes. The rate of major bleeding was 0.7% in patients receiving rivaroxaban in XALIA study and 0.8% in the EINSTEIN DVT study (15,16). Additionally, another study involving 5270 frail elderly patients with AF who were treated with warfarin or rivaroxaban demonstrated that over a period of over two years, rivaroxaban use led to a significant reduction in thrombotic events without causing a significant increase in major bleeding compared to warfarin (17). Similarly, in a study that analyzed electronic data from 35,613 obese patients with AF who were treated with either warfarin or rivaroxaban, the occurrence of thrombotic events and major bleeding over a period of 2.6 years were consistent with our findings, highlighting a significant reduction in bleeding events (18). However, the incidence of major bleeding in the warfarin and rivaroxaban groups (3.75 and 2.5%, respectively) was slightly elevated compared to the present study (3 and 2% respectively). This difference in findings could possibly be attributed to differences in sample size, duration of follow-up, and the increased risk of hemorrhagic complications in patients due to the presence of underlying diseases. Additionally, the lack of information about the target INR level among the patients may also play a role. The findings from a systematic review and meta-analysis aimed at investigating the risk of GI bleeding and intracranial hemorrhage in patients with AF using rivaroxaban or warfarin showed no significant difference between the two groups in terms of GI bleeding. However, the results indicated a lower risk of intracranial hemorrhage associated with rivaroxaban. Additionally, subgroup analysis, different patient characteristics, and past medical histories have revealed that warfarin poses a higher risk of bleeding in patients with end-stage renal diseases ($p=0.005$) (19).

However, the results of this study contradict some previous studies. A study conducted on 781 patients with stage 3 and 4 kidney failure, treated with rivaroxaban and 1536 patients treated with warfarin, revealed no significant difference in the occurrence of bleeding complications (20). This inconsistency could be explained by differences in patient characteristics between the two studies. Namely, the previous study included patients with AF and chronic renal failure, whereas the present study focused on a smaller sample of patients with a history of atrial fibrillation or pulmonary embolism without renal disease. Another study involving 4,848 patients with chronic renal failure and AF, who were treated with warfarin, as well as 1,896 patients treated with rivaroxaban,

similarly concluded that there was no significant difference in thrombotic events occurring with the use of either medication. However, it is worth nothing that a higher risk of major bleeding was observed in patients administered warfarin (21).

In previous studies, it was demonstrated that the impact and occurrence of side effects associated with rivaroxaban were significantly influenced by underlying diseases, age, and the sample size of the studies. However, the current study revealed that there is no significant difference in the occurrence of side effects between rivaroxaban and warfarin treatments in subgroups that also received other anticoagulant drugs like aspirin and clopidogrel.

In a recent study conducted on 100 patients with acute coronary artery disease and AF who underwent bypass surgery, the researchers compared the effects of rivaroxaban treatment to the standard treatments combined with clopidogrel. The results demonstrated no significant difference in the effectiveness of rivaroxaban and warfarin when administered alongside other antiplatelet medications. However, rivaroxaban exhibited a higher level of safety (22). These findings align closely with the outcomes of the current study.

This study had some limitations. The first was the inability to control the confounding factors that may have influenced the results. To address this in the future studies, it is recommended to use a stratified sampling method, considering factors such as age, underlying diseases, simultaneous use of other drugs, and specific drug subgroups. Moreover, the sample sizes in the subgroups were small and heterogeneous, potentially limiting the generalizability of the findings. Therefore, it is suggested that future researchers conduct cohort studies with larger sample sizes and utilize stratified sampling methods to ensure the validity of the results. Finally, the study's focus on patients receiving rivaroxaban and warfarin in emergency situations may have restricted the generalizability of the findings. While this allowed for a relevant assessment of bleeding risk in acute situations, cohort studies that investigate patients since the initiation of treatment may provide a more comprehensive understanding of the medications' long-term effects. By considering these limitations, the aim is to guide future research that can expand on these findings and provide more conclusive insights into the bleeding risks associated with these medications.

Conclusion

The results of this study suggest that prescription of rivaroxaban may lead to decreased complications and could be a safer treatment option for patients with a history of AF, pulmonary embolism, DVT or ischemic CVA when compared to warfarin. However, further studies are required to validate and confirm these findings.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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