Original Article

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Drug utilization evaluation of Rivaroxaban in both inpatient and outpatient settings: Using standard guidelines

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Abstract

Stroke-related atrial fibrillation (AF), deep vein thrombosis (DVT), and pulmonary thromboembolism (PE) are among the most common thromboembolic events. recently, direct oral anticoagulants (DOACs) have been slowly replacing warfarin. Rivaroxaban is a DOAC frequently prescribes to control thrombotic events. The safety and efficacy of Rivaroxaban are dependent on appropriate prescription, dosage, and other factors. This study is aimed to evaluate the Rivaroxaban utilization based on the standard protocol in both inpatient and outpatient settings. This cross-sectional/observational study was conducted for six months from 1st August 2018 to 1st February 2019 at a private hospital and also an outpatient clinic in Shiraz, Iran. First, a clinical pharmacist defined a standard protocol for Rivaroxaban utilization and several indexes (9 indexes for Non-valvular AF (NVAF) patients and 10 indexes for DVT/PE patients). Second, participants were classified into three groups (NVAF inpatients, NVAF outpatients, and DVT/PE patients). Finally, the adherence of Rivaroxaban utilization indexes in each group to was evaluated accordingly. Two hundred and forty one eligible patients were recruited into this study. Most patients (N=208), were NVAF. Rivaroxaban utilization was appropriate in 71.9%, 65.8%, and 50.6% of patients within groups 1, 2, and 3, respectively. Although medication interaction, administration regarding time/meal, and dose adjustment based on renal function showed the lowest compliance, the monitoring laboratory data and considering the underlying disorders were completely matched with the protocol. This study showed some critical errors in both settings, especially in DVT/PE patients (49.4% no match). Hence, the most productive collaboration must be developed between clinical pharmacists and clinical practitioners.

Keywords: Atrial fibrillation, Anticoagulants, Venous Thromboembolism, Pulmonary Thromboembolism, Rivaroxaban.

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1. Introduction

Thromboembolic disorders are considered a critical part of health problems worldwide. Following the increase in the number of elderly populations, the thrombotic disease prevalence has recently risen (1). Venous thromboembolism (including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and stroke-related atrial fibrillation (AF) are categorized in thromboembolic disorders, which can lead to multiple morbidities and also mortality (1, 2).

Anticoagulants are broadly prescribed to prevent and manage thromboembolic disorders (3). Warfarin and direct oral anticoagulants (DO-

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ACs) are among the most commonly used anticoagulants (4). Unlike warfarin, the prescription of DOACs has recently increased (5), in part owing to DOACs' potential in overcoming warfarin limitations such as its necessity for invasive monitoring, dose adjustment, and numerous food and drug interactions (6).

Rivaroxaban as a new DOAC agent inhibits directly factor Xa in both free and clot-bound forms (7, 8). Rivaroxaban possesses predictable pharmacokinetics. It is also more cost-effective than traditional anticoagulation therapy (9). Stroke prevention in non-valvular atrial fibrillation (NVAF) patients and DVT/PTE treatment are among the most prevalent Rivaroxaban indications (10).

Drug utilization evaluation (DUE) is a critical program in assessing rational drug use (11). Checking the drug indications and dose, administration course, drug-drug interaction (9), and observing the patients in their treatment duration are considered the essential DUE criteria (12). Hence, DUE programs assess healthcare settings' performances and reduce the cost of treatment by identifying and correcting errors immediately (13, 14).

As Rivaroxaban use has been increasing nowadays (15) and its prescription faced multiple challenges, such as delayed adverse effects, the risk of major bleeding without available neutralizing agents, and the requirement of dose adjustment based on liver/kidney function (15, 16), it is crucial to determine how Rivaroxaban is prescribed and used. Since the approval of Rivaroxaban in 2011, its usage has not been assessed adequately in Iran so far; therefore, this study aimed to evaluate Rivaroxaban utilization based on the standard protocol in both inpatient and outpatient health care settings.

2. Methods

2.1. Study design & Study setting

This cross sectional/observational study was performed during six months from 1st August 2018 to 1st February 2019 at different wards of Kowsar hospital, a private inpatient setting for cardiovascular diseases, and also a private clinic for outpatients' neurological disorders in Shiraz, Iran. The medical ethics committee of Shiraz University of Medical Sciences approved the study (IR.SUMS.REC.1398.338). All the protocols were in align with the ethical guidelines of the 1975 Helsinki Declaration (then amended in 2008). An informed consent form was obtained from each patient at the time of study entry. Any information was anonymized as much as possible.

2.2. Study population

The inclusion and exclusion criteria are listed as below:

2.2.1. Inclusion Criteria

- All newly inpatients or outpatients on Rivaroxaban regimen for preventing stroke and systemic embolism in the setting of NVAF or treatment of DVT/ PTE.

2.2.2. Exclusion Criteria

- Age less than 18 years
- Pregnancy and lactation
- Discontinuing Rivaroxaban or death in the first month of the treatment course
- Prescribing Rivaroxaban for other possible indications such as postoperative DVT thromboprophylaxis or management of Acute Coronary Syndrome

All subjects referred to hospital or an outpatient clinic while met inclusion criteria were enrolled in this study, and since all of them suffered from non-valvular AF (NVAF) or DVT/PTE, they were divided into three subgroups (Group I: Inpatients with NVAF, Group II: Outpatients with NVAF, Group III: patients with DVT/PTE). The duration of follow-up for each patient was 1 month.

2.3. Data gathering

In the first step, clinical pharmacists designed a standard protocol for Rivaroxaban utilization according to following references (Table 1):

Uptodate online

Applied Therapeutics: The Clinical Use of Drugs, 11th edition, 2018.

Pharmacotherapy: A Pathophysiologic Approach, 11th edition, 2020.

Braunwald's Heart Disease: A Textbook of

Table 1. The standard protocol of Rivaroxaban utilization.

Indications	NVAF	DVT /PTE treatment
Dosage	20mg QD	15 mg BID for 21 days followed by 20 mg QD
Dosing adjustment in renal impairment	CrCl>50 mL/minute: No dosage adjustment CrCl 15-50 mL/minute: 15 mg QD CrCl<15 mL/minute: Avoid	CrCl≥30 mL/minute: No dosage adjustment CrCl<30mL/minute: Avoid
Contraindications	Severe hypersensitivity to the medication or any ingredients of the formulation -Active bleeding -Also see the column of dose adjustment	
Rivaroxaban-Drug Interactions	Lexi-Interact Online (http://webstore.lexi.com/Lexi-Interact) See table 3.	
Pretreatment considerations	Renal function (SCr), CBC, LFT, and sign of bleeding	
Administration guide	Administer doses ≥15mg with food. For NVAF administer with the evening meal	
Monitoring	Education and documentation of Rivaroxaban side effects No routine coagulation testing	
CHA_2DS_2-VASc score in patients with AF	Candidate for receiving Rivaroxaban: CHA_2DS_2-VASc score ≥2 ,	

Required equations for Rivaroxaban utilization BMI (kg/m^2)=(Weight (kg))/(Height^2 (m)) Cockcroft-Gault Equation=[[140 - age(yr)]×weight(kg)]/[72×serum Cr(mg/dL)]

BMI: Body mass index, CBC: Complete blood count , CrCl: Creatinine clearance, DVT/PTE: Deep vein thrombosis/Pulmonary embolism, LFT: Liver function test , NVAF: Non-valvular atrial fibrillation, Scr: Serum creatinine.

Cardiovascular Medicine, 11th Edition, 2018).

The required information was gathered by both reviewing the patients' medical records and also face to face interviews with them. Demographic characteristics (age, sex, height, and total body weight), underlying diseases, anticoagulant regimen (indication, dose, and duration of administration), other medications, serum creatinine concentration (Scr), complete blood count (CBC) results, and liver function test (LFT) were recorded. Also, adverse drug reactions were documented after the first month of Rivaroxaban utilization. To identify potential drug-drug interactions (DDIs) between Rivaroxaban and other co-administered medications, Lexi comp drug interaction online version was used (http://webstore.lexi.com/Lexi-Interact).. Only type D or X DDIs were taken into account.

The Body Mass Index (BMI), glomerular filtration rate (calculated by Cockcroft-Gault equation) for all patients, and CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) (17) score for NVAF patients were individually calculated according to Table 1.

Finally, all indexes (18) of Rivaroxaban utilization were separately evaluated and compared with standard protocol in all three groups. These items were as follow:

1) Indication, 2) Monitoring of laboratory data (CBC, Renal and liver function), 3) Considering underlying disease, 4,5) Considering creatinine clearance to evaluate the drug dose adjustment and drug contraindication based on renal function, 6) Identifying a moderate or major interaction between Rivaroxaban and other co-administered medications by the Lexi-Interact online version 7) Patient education about side effects 8) Considering administration time of the day, 9) Monitoring the time interval of administration, 10) Notice to administration of drug regarding to meal , 11) Checking the type of administration (swallow, crush or chew) and 12) Considering CHA2DS2-VASc score in patients with AF to predict ischemic events. In addition to the mentioned items, patients with DVT and PE were also evaluated for dose and duration of primary and secondary courses of treatment.

2.4. Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation (SD) and percentage, respectively. The normal distribution

Table 2. Demographic data of the study population.

Demographic data	Gender	Group I (n=104)	Group II (n=104)	Group III (n=33)	All patients (n=241)
Age (yr)	Male (n=126)	65.45±15.9 (n=49)	67.39±14.63 (n=62)	61.53±20.13 (n=15)	66.90±15.20
	Female (n=115)	68.93±12.17 (n=55)	65.93±17.39 (n=42)	70.50±15.63 (n=18)	
Height (m)	Male	1.72±0.07	1.69±0.07	1.72±0.07	1.66±0.06
	Female	1.60±0.05	1.61±0.05	1.62±0.05	
Weight (kg)	Male	75.51±13.07	70.87±10.62	75.67±9.43	70.59±12.26
	Female	68.64±12.69	63.98±10.54	73.33±16.24	
BMI (kg/m2)	Male	25.40±4.07	24.80±3.00	25.43±3.02	25.59 ± 3.9
	Female	26.83±4.78	24.59±3.66	27.43±4.94	

BMI: Body mass index

of continuous variables was assessed by the Kolmogorov-Smirnov test. The comparison between continuous variables was performed by either independent t test (in the case of normal distribution) or Man-Whitney test (in the case of not normal distribution). P values less than 0.05 were considered to be statistically significant. All statistical analyses were performed in this study using Statistical Package for Social Sciences (SPSS) software version 20 (IBM Company, New York, United States).

3. Results

3.1. General characteristics

Initially, 280 inpatients and outpatients receiving Rivaroxaban were screened. Based on inclusion and exclusion criteria, 241 patients on the Rivaroxaban regimen were finally enrolled in the current study. They were classified into three groups, including group I (inpatients with NVAF, n=104), group II (outpatients with NVAF, n=104), and group III (patients with DVT/PTE, n=33). The demographic and anthropometric data of patients are classified and listed in Table 2. The mean ±SD age of the studied population was 66.90±15.20 years. More than half (52.28%) of the participants were male.

3.2. Monitoring laboratory data

Based on Table 3, the major laboratory data (CBC, Scr, and LFT) had been checked for all patients (100%) before (at baseline) and regularly during Rivaroxaban treatment.

3.3. Considering the underlying health disorders and contraindications

Hypertension (90.5%), dyslipidemia (43.2%), and diabetes (36.1%) were the most common underlying diseases in the study. Following hypertension, dyslipidemia (55.8%), stroke (43.3%), and diabetes (36.4%) were the most frequent underlying diseases in patients within group I, II, and III, respectively. There was no absolute contraindication to Rivaroxaban in all patients in three groups.

3.4. Rivaroxaban side effects

Rivaroxaban side effects were documented after the first month of starting the drug. The incidence of Rivaroxaban side effects are shown in Table 5. Non-major bleeding was the most common side effect among participants (9.1%). According to Table 3, all participants in groups II and III, and 99.0% of patients in group I were also educated about major Rivaroxaban side effects (bleeding).

3.5. Considering renal function

Regarding the importance of renal function status in Rivaroxaban recipients, two indexes were defined including dose adjustment and contraindications based on calculated GFR. In groups I & II, considering contraindications and dose adjustment based on calculated GFR were in align

Table 3. Comparison all indexes of Rivaroxaban utilization in the study with the standard Protocol.

Indexes	The compliance percentage with the Rivaroxaban utilization standard protocol		
	Group 1 (n=104)	Group 2 (n=104)	Group 3 (n=33)
Monitoring laboratory data	100	100	100
Considering underlying diseases	100	100	100
Education of Rivaroxaban side effects	99	100	100
Cr/Cl-based dose adjustment	60.6	56.6	
Cr/Cl-based contraindication	99	100	78.8
Major (level D&X) drug-drug interaction	29.8	46.2	30.3
Administration Time of the day	2.9	22.1	6.1
Drug administration regarding meal	66.3	78.8	57.6
Considering CHA2DS2-VASc score	89.4	88.5	
Dose in the primary course of DVT/PTE treatment			54.5
Duration of the primary course of DVT/PTE treatment			42.4
Correct administration in DVT/PTE treatment			36.4
Total compliance with standard protocol	71.9	65.8	50.6

BMI: Body mass index, CrCl: Creatinine clearance, DVT/PTE: Deep vein thrombosis/Pulmonary embolism.

with standard guideline in 99.5% and 60.1% of cases, respectively. In group III, more than three-fourth (78.8%) of Rivaroxaban administrations were appropriate according to its contraindications regarding calculated GFR.

3.6. Major DDIs of Rivaroxaban

The potential DDIs of Rivaroxaban was evaluated in all three groups. The type, frequency, severity, and the probable mechanism of Rivaroxaban DI were summarized in Table 4. Aspirin and carbamazepine were the most common drugs that had type D and X interactions with Rivaroxaban, respectively. The mean number of type D and X DDIs in groups I and II was 0.34±0.13 and 0.14 ± 0.02, respectively. This difference reaches the level of statistical significance (p=0.003).

3.7. Rivaroxaban administration regarding meal and time of the day

The Rivaroxaban administration regarding meal and time of the day were assessed for all patients. Although the recommended time for the administration of Rivaroxaban is with the evening meal, only 11.6% of the study population was taking their drug in the evening, and most patients have preferred bedtime medication (39.4%). Besides, 70% of the Rivaroxaban recipients took the drug with a meal.

3.8. CHA2DS2-VASc score

The CHA_2DS_2-VASc score was calculated in NVAF patients for estimating stroke risk. Its mean ± SD score was 3.15±1.81 and 4.40±1.81 in males and females, respectively. According to Table 3, the percentage of this index with the standard protocol was 89.4% and 88.5% in groups I and II, respectively.

3.9. DVT/PTE treatment

The course of DVT/PTE treatment by Rivaroxaban is divided into two periods including primary (15mg BD for 21 days) and secondary courses (20mg QD for at least 3 months). The dose and duration of initial treatment phase with Rivaroxaban were correct in 51.9% and 40.7% of DVT patients, respectively. The corresponding values were 66.7% and 50% for patients with PTE, respectively. In the maintenance treatment phase, Rivaroxaban was properly dosed only in one-third (33.3 %) of patients with DVT and half of those (50 %) with PTE.

Table 4. Rivaroxaban-drug interactions in all patients.

Type	Rivaroxaban-drug interactions	Frequency (n)	Possible mechanism
D	Aspirin	86	↑Adverse/toxic effect
	Naproxen	24	
	Clopidogrel	21	
	Diclofenac	15	
	Meloxicam	9	
	Ibuprofen	6	
	Ketorolac	5	
	Verapamil	3	↑ Rivaroxaban serum concentration
X	Carbamazepine	7	↓ Rivaroxaban serum concentration
	Phenobarbital	5	
	Phenytoin	3	
	Enoxaparin	3	↑ Anticoagulant effect

3.10. Total compliance percentage with the standard protocol of Rivaroxaban utilization

According to Table 3, the total compliance rates of groups I, II, and III with the standard protocol of Rivaroxaban utilization were 71.9%, 65.8%, and 50.6%, respectively. The difference between the mean sum of studied indexes of Rivaroxaban use in patients in groups I and II (9.4±6.9 and 12.1±9.3, respectively) was statistically significant (p=0.004). In other words, attention to standard guideline of Rivaroxaban use in patients with NVAF was higher in private offices than inpatient settings.

4. Discussion

The current research has highlighted that Rivaroxaban's inappropriate utilization is common in AF and DVT/PTE patients. The most frequent inappropriate indexes of Rivaroxaban utilization were the Rivaroxaban administration regarding time and meal, major Rivaroxaban DDI, and considering renal function. On the other hand, monitoring laboratory data, considering underlying diseases, and Rivaroxaban side effect indexes almost complied with standard protocol. According to previous DUE studies, inappropriate dosing and therapy duration were the most frequent Rivaroxaban utilization problems (20-22).

NVAF and DVT/PTE are among the main Rivaroxaban indications (10). From all patients (n=241) were enrolled in our study, most of them (N=208, 86.31%), received Rivaroxaban for NVAF with 100% appropriate indication. The Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) which has investigated newly diagnosed AF patients in various countries, noted that the NVAF worldwide prevalence has been linked to population longevity. As elderly populationis growing, the prevalence of AF is expected to increase (23). Therefore, the high percentages of such indication for Rivaroxaban in our study may also be related to expanding longevity in Iranian population. Another prospective cross-sectional research recently carried out on 104 participants in Isfahan, Iran, reported that the most common indication (37.5%) of this anticoagulant was DVT prophylaxis. It also noticed that about 34% of rivaroxaban prescriptions was correct and the most faults were in terms of dose (50.9%) and duration of treatment (71.4%) (22). In alignment with our findings, the most frequent errors associated with dosing and duration of treatment were amongst the patients with DVT/PTE, that 45.5% and 57.8% of them were received incorrect dose and duration of treatment, respectively. In contrast to these findings, a retrospective chart review using the system's electronic medical records at eight health system hospitals in the United States demonstrated that among 62 patients receiving Rivaroxaban, the indication was correct in 82% of cases. In addition, 92% of participants were received the appropriate

Table 5. Rivaroxaban adverse effects in the study population

	Adverse effect	Group I		Group II		Group III		All the patients
		Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
1	Non-major bleeding	8	7. 7	9	8. 7	5	15. 2	22 (9.1%)
2	Insomnia	6	5. 8	5	4. 8	0	0	11 (4.6%)
3	Abdominal pain	6	5. 8	3	2. 9	2	6. 1	11 (4.6%)
4	Wound secretion	5	4. 8	3	2. 9	2	6. 1	10 (4.1%)
5	Constipation	4	3. 8	3	2. 9	2	6. 1	9 (3.7%)
6	Pruritus	4	3. 8	1	1	1	3	6 (2.5%)
7	Major bleeding	3	2. 9	1	1	1	3	5 (2.1%)
8	Diarrhea	3	2. 9	2	1. 9	0	0	5 (2.1%)
9	Dizziness	1	1	3	2. 9	0	0	4 (1.7%)
10	Anxiety	0	0	1	1	1	3	2 (0.8%)

dose of rivaroxaban (24).

Most candidates for anticoagulants are an elderly population that usually be on the polypharmacy regimens for their various underlying diseases (25). According to our study, the mean age of all participants was 66.90±15.20 years. Therefore, the risk of major DDI and side effects are more critical to be evaluated in these patients. In our study, the number of DDIs were higher in the inpatient compared to the outpatients. This is mostly due to the fact that all inpatients were under polypharmacy and they may have more comorbidities. In line with this finding, a systematic review of literature about DDIs in Iran demonstrated that the median incidence of potential DDIs in outpatient and inpatient settings was 8.5% per prescription and 19.2%, respectively.

Compared to vitamin K antagonists (e.g., Warfarin), DOACs (e.g., Rivaroxaban) have a superior safety profile with fewer major bleeding episodes including intracranial bleedings and hemorrhagic strokes (23, 26). The risk of major and non-major Rivaroxaban bleeding was reported about 0.3% and 11%, respectively, by a meta-analysis (27), which are almost similar to our study (1% major and 9.1% non-major bleeding). A number of variables have been reported to be risk factors of Rivaroxaban bleeding such as increased age, uncontrolled hypertension, and concomitant treatment with antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs), or paracetamol (28). DOACs-related major bleeding episodes are considered as emergency and needs to control immediately. Beside general supportive therapy, Andexanet alfa, a specific antidote, has been approved for the management of uncontrollable bleeding episodes due to rivaroxaban (29).

The GI absorption and renal excretion of DOACs are affected by P-glycoprotein (P-gp) transporters and cytochrome (CYP) 3A4 enzymes. Therefore, the inducer and inhibitors of CYP3A4 and P-gp systems can potentially interact with DOACs (30). In our study, the most frequent D-type Rivaroxaban DDIs involved with aspirin, naproxen, and clopidogrel. The most common X-type Rivaroxaban DDIs were carbamazepine, phenobarbital, and phenytoin. These antiepileptic agents are strong inducers of CYP enzymatic as well as P-gp systems and their co-administration can decrease Rivaroxaban AUC, leading to anticoagulant failure (31). The combination of DOACs with antiplatelet drugs and/or NSAIDs is quite common in clinical practice (32). Interestingly, most bleeding events were documented in the literature when antiplatelet agents are prescribed simultaneously with oral anticoagulants such as Rivaroxaban (31, 33).

Rivaroxaban is mainly excreted by the kidneys; therefore, either avoidance or dose adjustment should be considered in Rivaroxaban prescription in the setting of renal insufficiency. Underdosing and overdosing of Rivaroxaban can

potentially put patients at the risk of treatment failure (e.g., thromboembolic events) and toxicity (bleeding episodes), respectively. Based on a 5-year, cross-sectional, retrospective study in Qatar, 33.6% of DOACs prescriptions hold inappropriate dosing (34). In another observational study on hospitalized patients in Belgium, 20% of AF patients received inappropriate dose of Rivaroxaban based on their renal function (35). Mousavi and et al. also indicated that only 50% of participants used adjusted doses regarding serum CrCl (22). These findings are almost similar to our study, in which the inappropriate renal-based dose adjustment occurred in 60.6% and 56.6% of NVAF inpatients (group 1) and outpatients (group 2), respectively.

In our study, the administration of Rivaroxaban regarding food and time of the day was not correct in up to 42.4% and 97.1% of the participants, respectively. Concerning the effect of food on the absorption and pharmacokinetics of Rivaroxaban, oral bioavailability of doses up to 10 mg Rivaroxaban were independent of food. In contrast, high bioavailability (≥80%) of 15 mg and 20 mg Rivaroxaban was achieved when taken with food; therefore, it has been stated that 15 mg and 20 mg Rivaroxaban should be taken with food (36). It has been also recommended that Rivaroxaban should be administered with regard to the evening meal.

The current survey suffers from a number of drawbacks. Firstly, this study was conducted in private healthcare settings; therefore, public clinics and hospitals must be investigated in future studies. Second, since NVAF patients were assigned from two medical centers with different indication , it was impossible to compare physicians' performance in the hospital and the clinic. Third, since the DOACs may have delayed side effects, a meticulous and prolonged follow up process must be considered in future investigations. Lastly, other possible indications of Rivaroxaban including postoperative DVT thromboprophylaxis and also management of Acute Coronary Syndrome did not taken into consideration in this study. This is mostly due to the fact that the former indication of Rivaroxaban was related to outpatients undergone certain orthopedic surgeries. The latter indication of Rivaroxaban was somewhat new and had not been generally applied in the study settings prior to our investigation. In addition, regarding the fact that this study was conducted before COVID-19 outbreak, assessment of Rivaroxaban use for DVT thromboprophylaxis in COVID-19 patients was not feasible.

5. Conclusion

Rivaroxaban utilization evaluation in our study suggests prescribing patterns are not compatible with the standard protocol especially in patients with DVT/PTE. The total compliance rate of Rivaroxaban utilization in NVAF inpatients, NVAF outpatients, and patients with DVT/PTE compared to the standard protocol were 71.9%, 65.8%, and 50.6%, respectively. In patients with NVAF, the total compliance rate of Rivaroxaban utilization is higher in outpatients than inpatients setting. Physicians should be more vigilant and pay more attention to dose adjustment of Rivaroxaban based on renal function of patients, its major DDIs, and appropriate administration of Rivaroxaban regarding food and time of the day.

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Conflict of Interest

None declared.

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