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Original Article

Utilization and Prescribing Pattern of Rivaroxaban in a Large Teaching Hospital in Iran

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Abstract

This medication utilization evaluation aims to describe the use of rivaroxaban in a tertiary care teaching hospital and to audit the hospital physician's prescribing practice. A prospective cross-sectional study was performed from March to December 2019 in Alzahra teaching hospital, Isfahan, Iran. All patients who received at least one dose of rivaroxaban were eligible for inclusion. Data were collected on patient demographics, indication, dosing regimen, adverse events, concurrent anticoagulant therapy, and laboratory tests (including renal function). A total of 104 patients were included in our study. Most patients (N=39, 37.5%) were prescribed rivaroxaban for deep vein thrombosis (DVT) prophylaxis. Overall, more than 34% of rivaroxaban prescriptions was appropriate. Rivaroxaban was indicated correctly in all the patients (100% appropriate indication). However, 58.6% and 50% of patients received correct dosing, respectively, based on indication and renal function. High-dose prescribing was the major fault of prescriptions when the renal function was taken into account (82.6%). An appropriate switch occurred in 48.7% of the patients who switched from one anticoagulant to another. Inappropriate prescription of rivaroxaban for many patients in the current study emphasizes the requirement of developing a scientifically well-defined protocol for the use of rivaroxaban in the evaluated hospital. Accordingly, establishing a structured educational program for prescribers and assigning the rivaroxaban prescription to specialized services with consultation with clinical pharmacists is recommended.

Keywords: Clinical Audit, Medication-Utilization-Evaluation, Rivaroxaban.

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1. Introduction

New oral anticoagulants included rivaroxaban, apixaban, and edoxaban are potential replacements for warfarin therapy. These drugs overcome warfarin-therapy challenges, including frequent monitoring,

numerous drug interactions, delayed onset time, and narrow therapeutic index [1, 2].

Rivaroxaban was approved for the prevention of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery, prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF), also, for the treatment of DVT and pulmonary embolism (PE) and to reduce the risk of DVT and PE recurrence [3, 4, 5].

Rivaroxaban is a highly selective direct Xa factor inhibitor with a rapid onset of action. It can be absorbed rapidly with maximum plasma concentration achieved within 2-4 hours. The oral bioavailability decreases with higher doses and increases when taken with food. The pharmacokinetics profile of the drug is predictable according to age, gender, weight and race [6]. The drug has a half-life of 5-9 hours in healthy individuals (age 20-45) and 11-13 hours in elderly persons. Approximately two-thirds of the dose of this drug is metabolized through CYP3A4, CYP3A5, and CYP-independent mechanisms [7]. Two-thirds of rivaroxaban is excreted into urine and the remaining in the feces. Thus the dose adjustment is required in patients with a creatinine clearance (CrCl) of less than 50ml/min [8].

Co-administration of rivaroxaban with potent p-glycoprotein inhibitors/inducer and CYP3A4 inhibitors/inducer should be avoided as this might increase the risk of bleeding and thromboembolism [9].

The most serious adverse effect of rivaroxaban is bleeding. Rates of fatal bleeding events is less in rivaroxaban users compared to warfarin, but, rivaroxaban is associated with higher rates of gastrointestinal bleeding [10]. Post-marketing assessments (in 2015) showed liver toxicity with the use of rivaroxaban which resulted in contraindication of this drug in patients with significant liver diseases (child-pugh class B or C) and end-stage renal disease [11].

Although, a reversal agent for rivaroxaban is now available (Andexanet Alpha) but its safety and efficacy is not as clear as the older reversal agents (such as vitamin K). This means that serious bleedings might be more difficult to manage [12]. Also, lack of laboratory parameters for rivaroxaban, makes it difficult to manage rivaroxaban dosage in case of drug interactions or in especial populations (e.g. elderlies, obese patients, or those with renal dysfunction). Table 1 shows rivaroxaban dosing recommendation.

Rivaroxaban is available in the Iranian market in three different strengths: 10, 15, and 20mg tablets, however there is no publication on its prescription in hospitals in the country. Unfortunately, there is not any guidance or order set to initiate therapy with rivaroxaban. Therefore, it is crucial to assess its use within the clinical setting to ensure appropriateness of the prescription, safety, efficacy and diagnosis of improvement.

For newly approved drugs such as rivaroxaban, medication use evaluation (MUE) is strongly recommended to evaluate physicians' prescribing behavior and provide information for health care system planning. This MUE aimed to describe how rivaroxaban was prescribed in a tertiary care teaching

hospital and to audit the hospital physicians prescribing practice.

2. Materials and Methods

This prospective cross-sectional study was conducted in Alzahra hospital, an 850-bed educational hospital with inpatient and outpatient care services, affiliated to Isfahan University of Medical Sciences (IUMS), Isfahan, Iran. All patients who received rivaroxaban (even a single dose) from March to December 2019 were identified and included in the study using the pharmacy computerized information system. The charts of each patient were reviewed, and data were retrieved. All included patients followed up until discharge or death. Institutional review board approval was obtained from IUMS with project number (397613).

A data collection standard form was developed, pretested, and modified prior to data collection, including patient demographic details (gender, age, weight, etc.), diagnosis at the admission, admission unit, dates of admission and discharge, prescribing data of rivaroxaban (including indication, dose, dosing interval, route of administration and duration of therapy), details of other anticoagulant therapy, before or concomitant with rivaroxaban, (including the agent, dose, duration of therapy and transitioning between anticoagulants), laboratory data (including hemoglobin and platelet count, PT, aPTT, INR, AST, ALT, Albumin and serum creatinine), documented bleeding or thromboembolism, and patient's final outcome (dead or alive). Serum creatinine was used to assess renal function by calculation of creatinine clearance (CrCl), utilizing the cockroft-gault equation. The appropriateness of dosing and switching between the medications was evaluated based on the recommendations of the manufacturer (presented in Table 1).

The appropriateness of the initial-regimen order was assessed according to the rivaroxaban indication, dose, frequency and appropriate transition. The manufacturer's recommendation and Lexi-comp drug information were used to determine the appropriateness of the use of rivaroxaban.

The categorical variables were expressed as frequencies and percentages while continuous variables were expressed as means and standard deviations (SDs). SPSS 20.0, Chicago, USA software was used to perform calculations.

3. Results and Discussion

A total of 104 patients received rivaroxaban during the study period. The mean age was 65.7±19.8 (range: 17-94 years). Male subjects constituted 54.8% (N=57) of patients. The most frequent admission diagnosis included cerebrovascular accidents (N=18), PTE (N=17), DVT (N=12), and congestive heart failure (N=6). Most of the patients were admitted to the pulmonary and neurology wards. Table 2 presents the baseline characteristics of the patients.

Rivaroxaban prescription characteristics are shown in Table 3. 39 (37.5%) of the patients received this drug for DVT prophylaxis.

NVAF was the second most common indication (23.1%, N=24). The 15mg tablet was the most prescribed dosage form (65.4%, N=68). More than half of the patients (66, 63.5%) received rivaroxaban once daily. All the patients received rivaroxaban for approved indications. Almost half of the patients received rivaroxaban for a duration of less than a week, while the shortest treatment length is 35 days, according to the manufacturer's recommendation.

64 patients (61.5%) had a CrCl of greater than 50ml/min. The majority of the prescribers were neurologists (27, 25.9%) and pulmonologists (17, 16.3%). 6 (5.8%) of the patients died during the study period. Thirty patients (18.8%) had drug-drug interactions, in which 28 (22.1%) of them the drug interactions were of class-D (e.g., aspirin, amiodarone).

The results of the appropriateness of rivaroxaban prescribing are reported in Table 4. Thirty-four patients (32.7%) received rivaroxaban with appropriate indication, dose, and duration. Rivaroxaban was adjusted appropriately according to CrCl in 52 patients (50%). According to approved indications, the dose was appropriate in 61 patients (58%). Overall, the dose was appropriate (based on both indication and renal adjustment) in 53 patients (50.9%). Neurologists (27/104), pulmonologists (17/104), surgeons (14/104), and cardiologists (14/104) were the medical specialty mainly prescribed rivaroxaban. Surgeons (71.4%) followed by neurologists (61.6%) had the most error inaccurate dose adjustment according to renal function.

Table 5 shows the concurrent anticoagulant therapy with rivaroxaban. In 50 of the patients (48.7%) the prescribed transitions were appropriate, while in two patients, the transitions were inappropriate (from warfarin to rivaroxaban with INR>3).

Thirteen patients had thrombocytopenia during the treatment with rivaroxaban. In 5 cases platelet count increased after rivaroxaban initiation. In 6 cases, the platelet levels decreased and in 2 cases remained unchanged.

One case of minor bleeding and one thrombosis were reported after rivaroxaban administration.

3.1. Discussion

Results of the current study show that rivaroxaban was prescribed for appropriate indications in all, but the most frequent issues were the inappropriateness of the rivaroxaban dose prescription (50.9%) and the inappropriate duration of treatment (71.4%). Overall, one-third of the patients received rivaroxaban with appropriate indication, dose, and duration of treatment.

Consequently, although the prescribers have been familiar with the indications of rivaroxaban therapy, their information, especially about the appropriate dosage and duration of the evaluated drug, is low or incomplete. In the current study, Rivaroxaban was mainly prescribed to prevent DVT and prevent stroke in NVAF. Rivaroxaban does not need regular monitoring and adjustment of INR despite warfarin; therefore, it is a reasonable and suitable option for the

prescribers, particularly in the indications that need long-duration therapy (e.g., prophylaxis of DVT).

Appropriate dose and duration of treatment are necessary for drug efficacy which has been inappropriate in our study. Only half of our patients received appropriate doses of rivaroxaban when their renal function was taken into account, with the majority of these doses (82.7%) higher than the current prescribing recommendation. Duration of treatment was inappropriate in 70% of the patients. Only 3.8% of patients received rivaroxaban for more than one month, the shortest treatment length based on the manufacturer's recommendation (at least 35 days). Mayet *et al*. performed an MUE with a similar design to our study in a tertiary teaching hospital. Among the 322 patients who received rivaroxaban< >56% of them had at least one inappropriate criteria of prescription [14]. In their study, 24.8% of the patients received rivaroxaban for inappropriate indications, while all received this drug with approved indications. In addition, less than half of the patients (41.7%) in the Mayet *et al*. study received rivaroxaban with appropriate dosage, and dose-adjustment according to renal function was performed in 58% of the patients and the majority of these doses was lower than current prescribing recommendations. This was not similar to the current study. However, our results concur with the results of this study regarding the dose-adjustment. Also, the results of this study concur with the Withworth *et al*. study, which demonstrated that 34.8% of patients on rivaroxaban received inappropriate dosing (although mostly lower doses) [15]. Tellor *et al*. reported an inappropriate dose prescription of 35.4% in patients who received rivaroxaban for NVAF [16]. Our results align with this study regarding the inappropriateness of dose, which confirm the lack of drug information in our prescribers and emphases on the requirement of the educational programs for them. Conversely, some studies reported appropriate dosing of rivaroxaban. In Isaacs *et al*., study, 92% of rivaroxaban patients received correct dosing based on indication and renal function [17]. Another study by Chowdhry *et al*., showed that only 2% of rivaroxaban prescriptions were associated with inappropriate high doses. It seems that in these studies physicians followed a system protocol for prescribing rivaroxaban, which significantly reduced the error in dosing, indication, and other criteria of appropriate prescribing [18]. Unfortunately, in our hospital, physicians do not follow any system protocol and do not pay enough attention to the manufacturer's recommendations regarding the appropriate prescriptions of rivaroxaban as well. Although the indications were appropriate in all of our patients, the lack of an accurate dose and duration might reduce the efficacy of rivaroxaban and increase its adverse effects, which end in incomplete care of the patients. Also, inappropriate prescribing of rivaroxaban increases systemic costs, considering its acquisition cost in our setting. Our center must develop a protocol and appropriate education programs for clinicians

regarding the indication, dosing, adverse effects, and contraindications of rivaroxaban.

Appropriate transition occurred in 48% of the cases for patients transitioning to or from another anticoagulant. The same percentage was reported by Isaacs *et al*., study [17]. Appropriate transition between anticoagulant-therapies can reduce the risk of thromboembolism and bleeding. Initiating the administration of rivaroxaban too early after discontinuation of previous therapy enhances the risk of bleeding. In the current study, we found two cases on warfarin and received rivaroxaban when INR was more than 3. Although the bleeding did not occur in these cases, it shows that our practitioners had low experience with this new anticoagulant. It is vital to educate them on proper transitions between anticoagulants to enhance the safety and effectiveness of this new anticoagulant rivaroxaban.

Thirteen of our patients had thrombocytopenia during treatment with rivaroxaban. In five cases, platelet level increased, and in 6 cases decreased. Although these patients had underlying diseases that described the causes of thrombocytopenia, this condition could increase the risk of bleeding with rivaroxaban. However, it is not a contraindication for rivaroxaban prescription. Mousavi *et al*. [19] performed an MUE on dabigatran in which 36 patients out of 60 had thrombocytopenia (heparin-induced) at the time of dabigatran initiation. In their study, platelet levels increased in 32 patients after dabigatran initiation. Consequently, they proposed dabigatran as an alternative agent in treating heparin-induced thrombocytopenia. We did not observe the same pattern in our patients and even in cases in which platelet increased. This might be due to the improvement of underlying diseases and not the actions of rivaroxaban.

Regarding medical specialty, neurologists, followed by pulmonologists, prescribed rivaroxaban for approved indication, mostly. The neurologists prescribed rivaroxaban for prophylaxis of DVT (11 out of 27 prescriptions) and pulmonologists for treatment of PTE (8 out of 18 prescription). Our surgeons prescribed this drug for DVT prophylaxis (8 out of 184 prescription), but in 10 of the 14 cases (71%), the prescribed dose was inappropriate, and dose adjustment was not made according to renal function. 66.6% of the prescriptions of the neurologists were inappropriate due to the use of incorrect doses (lack of adjustment). In Mayet *et al*., study, cardiologists and hematologists had the highest rates of rivaroxaban prescribing and inappropriate prescribing [14]. Although, in their study rivaroxaban prescription was restricted to specialized services such as cardiologists and orthopedic surgeons. The prescription of rivaroxaban is not restricted in the Alzahra center, leading to a high rate of prescriptions and inappropriateness. This finding confirms the importance of establishing a structured educational program for prescribers and restricting the prescription of this drug to specialized services and consultation with clinical pharmacists.

Our study limitations are as follows: first, this was a mono-centric study with a relatively small number of prescriptions within a short duration of time. Second, we had no proper documentation of rivaroxaban adverse effects.

4. Conclusion

In conclusion, overall, 34% of appropriate rivaroxaban prescription in our study indicates that this protocol should be evidence-based and enlighten physicians about the appropriate way to prescribe rivaroxaban, considering correct indications and dosing per CrCl. Restriction of rivaroxaban prescribing to specialty services and performing educational programs is needed to increase rational use of this drug and patient safety. Further research is required to fully elucidate the consequence of inappropriate rivaroxaban prescribing and the impact of interventions on improving rivaroxaban prescribing.

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Tables:

Table 1. Rivaroxaban dosing and transitions between anticoagulants recommendations.

Indication	**Renal function**	**Dosage**
Reduction in risk of stroke and systemic embolism in nonvalvular AF	CrCl > 50 ml/min	20 mg orally daily
	CrCl 15-50 ml/min	15 mg orally daily
Treatment of DVT and PE	CrCl > 50 ml/min	15 mg orally q12hr for 21 days, THEN 20 mg orally daily
	CrCl 30-50 ml/min	15 mg orally q12hr for 21 days, THEN 15 mg orally daily
Prophylaxis of DVT	CrCl >30 ml/min	10 mg orally daily, in hospital and after hospital discharges, for 31-39 days
Prophylaxis of DVT and PE following hip/knee replacement surgery	CrCl >30 ml/min	10 mg orally daily

Switching to rivaroxaban

- From warfarin to rivaroxaban: Discontinue warfarin and start rivaroxaban as soon as INR <3
- From anticoagulant other than warfarin (e.g., low molecular weight heparin) to rivaroxaban: Start rivaroxaban 0-2 hrs prior to next scheduled evening administration and omit administration of the other anticoagulant
- From unfractionated heparin continuous infusion to rivaroxaban: Stop infusion and start rivaroxaban at the same time

Switching from rivaroxaban

- From rivaroxaban to warfarin: No clinical data available; INR measurements during co-administration with warfarin may not be useful for determining appropriate dose of warfarin; one approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at time the next scheduled dose of rivaroxaban
- From rivaroxaban and transitional to rapid-onset anticoagulant: Discontinue rivaroxaban and give first dose of other anticoagulant (orally or parenteral) at the next scheduled rivaroxaban dose

CrCl: Creatinine clearance, BID: twice daily, AF: Atrial-Fibrillation, DVT: Deep-Vein-Thrombosis, PE: Pulmonary-Emboli, INR: International-Normalization-Ratio.

Table 2. Baseline patients' characteristic.

Characteristics	**Number of patients (N=104)**
Age, year (range)	Mean: 65.7±19.8 (17-94)
Sex, male (N) (%)	57 (54.8)
Length of hospital stay (Days) (range)	16.2±19.4 (3-176)
Admission diagnosis	
CVA	18
PTE	17
DVT	12
CHF	6

COPD	4
Pleural effusion	4
Pneumonia	3
Multiple trauma	3
Atrial fibrillation	3
Urinary tract infection	3
Sepsis	2
Coronary artery bypass grafting	2
Gastrointestinal bleeding	2
Pulmonary hypertension	2
Others	23
Laboratory data	
Platelet (mean)	164200±79480/mm^3
Prothrombin time (PT) (mean)	16.5±8.2
Partial thromboplastin time (PTT) (mean)	39.2±15
Hemoglobin (mean)	11.7±2.3 g/dl
AST	54.1±121
ALT	61.7±161
Albumin	3.3±0.57g/dl
Survival, N (%)	
Death	6 (5.8)
Alive	98 (94.2)
Admission wards, N (%)	
Pulmonary	16 (15.4)
Neurology	14 (13.5)
Cardiology	11 (10.6)
Intensive care unit	9 (8.7)
Cardiac care unit	8 (7.7)

CHF: Congestive-Heart-Failure, COPD: Chronic-Obstruction-Pulmonary-Disease, CVA: Cerebro-Vascular-Accident, DVT: Deep-Vein-Thrombosis, PTE: -Thrombo-Embolism.

Table 3. Indications for use of rivaroxaban.

Variables	**Patients (N=104)**
Nonvalvular atrial fibrillation	24 (23.1%)
Treatment of PE	20 (19.2%)
Treatment of DVT	14 (13.5%)
Prophylaxis of DVT	39 (37.5%)
Prophylaxis of PE	7 (6.7%)
Dose, N(%)	
10 mg	8 (7.2)
15 mg	68 (65.4)
20 mg	28 (26.9)

Interval, N(%)	
Daily	66 (63.5)
Twice daily	38 (36.5)
Duration of treatment (days), mean±SD, range	8.8±9.3 (2-50)
Less than a week, N(%)	51 (49)
One week to one month	49 (47.1)
> 1 month	4 (3.8)
Laboratory data	
Platelet	
At initiation	182191.2±81827.8 (35000-382000)/mm^3
During treatment	181346.5±73971.1 (33000-480000)/ mm^3
Mean of INR	
At initiation	1.7±1.3 (1-10.6)
During treatment	1.8±1.5 (1.1-12.4)
Mean of PT during treatment	17.2±1.5 (10.4-65.9)
Mean of PTT during treatment	36.7±9.8 (27-75)
Mean of SrCr during treatment	1.1±0.3 (0.5-2.1) mg/dl
Creatinine clearance	
ClCr >50ml/min, N (%)	64 (61.5)
ClCr 30-50 ml/min	32 (30.8)
ClCr <30 ml/min	8 (7.7)
Prescribers, N(%)	
Neurologist	27 (25.9)
Pulmonologist	17 (16.3)
Cardiologist	14 (13.5)
Surgeons	14 (13.5)
Infection specialist	11 (10.6)

DVT: Deep-Vein-Thrombosis, INR: International-Normalized-Ratio, PE: Pulmonary-Emboli, PT: Prothrombin-Time, PTT: Partial-Thromboplastin-Time, SrCr: Serum-Creatinine.

Table 4. Audit of rivaroxaban prescriptions based on appropriate criteria.

Appropriate criteria	**N (%)**
Overall appropriateness (N=104)	34 (32.7)
Appropriateness according to dose	53 (50.9)
Per CrCl	52 (50)
Inappropriate lower dose	3 (5.8)
Inappropriate higher dose	43 (82.7)
Contraindicated (CrCl <30ml/min)	6 (11.5)
Per indication	61 (58.6)
Per interval	86 (82.7)
Appropriate duration of treatment	74 (71.1)
Appropriate according to medical specialty	(inappropriate dose/total prescription)
Neurologists	18/27 (66.6%)

Pulmonologists	5/17 (29.4%)
Surgeons	10/14 (71.4%)
Cardiologists	7 (14) (50%)
Infection specialists	3/11 (27.2%)

CrCl: Creatinine-Clearance

Table 5. Concurrent anticoagulant therapy with rivaroxaban.

Drug	**Before rivaroxaban initiation**	**Concurrent with rivaroxaban**	**After rivaroxaban**	**Appropriate transition**
Unfractionated heparin	36	15	3	24
Enoxaparine	26	8	1	26
Warfarin	11	4	0	11