

ORIGINAL ARTICLE

Non-Adherence Factors Associated with the Use of Rivaroxaban Among Patients with Deep Venous Thromboembolism: A Single Center Observational Study

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ABSTRACT

Purpose: To assess the rate and factors associated with non-adherence of Rivaroxaban in patients with deep venous thrombosis.

Methodology: An observational longitudinal study was conducted at the Department of Surgery, Aga Khan University & Hospital, Karachi between June 2022 to November 2022. Patients with known malignancy with or without chemotherapy, those with a known diagnosis of hypercoagulability disorder or a history of limb trauma leading to deep venous thrombosis were included in the study. Patients who have refused to start rivaroxaban treatment prescribed by vascular surgeons, those with cognitive disabilities, such as dementia, who need to rely on a caregiver for their medical care were excluded. The frequency of missed doses, side effects, and causes of non-adherence to the prescribed treatment were recorded.

Results: A total of 180 patients were recruited with a mean age of 66.3 ± 8.2 years. Out of 180 patients, 111 (61.6%) missed at least one dose during treatment. We reported the self-reported adherence of 70%. 72 (30%) were non-adherent. Majority revealed that they forget to take medicine; 78 (43.3%) or experienced side effects; 60 (33.3%). Five patients were hospitalized due to serious adverse events (bleeding per rectal and gastrointestinal).

Conclusion: A significant percentage of non-adherence among participants was found in our study. One of the primary causes of non-adherence was forgetfulness. We recommended that patients get appropriate counseling on the expected results and negative effects of the medicine in order to promote adherence to Rivaroxaban.

Keywords: Adherence, compliance, deep venous thrombosis, Rivaroxaban

INTRODUCTION

Rivaroxaban is a direct oral anticoagulant (DOAC).¹ It is anti-atherogenic and exhibits antiplatelet activity by indirectly down regulating platelet activation receptors.² Studies in various countries suggest that patients were unfamiliar with the safety profile and more minor drug interactions of DOAC versus vitamin K antagonists.³⁻⁹ Non-adherence was reported more in elderly patients with multiple comorbidities.¹⁰ Some measures have been proposed such as the use of text messages reminders, less frequent doses regimen, continuous education of patients and their relative's, educational brochures, and pill organizers were proposed to improve drug therapy adherence among patients currently on DOACS.³

Rivaroxaban is a direct oral anticoagulant (DOAC).¹¹ It has been studied vigorously in the last decade after which it has become a reliable drug for primary and secondary prevention of disease processes such as peripheral arterial disease, deep venous thrombosis, and stroke.¹² It works by directly blocking the factor Xa (thrombin) in the clotting cascade. Moreover, evidence suggests, it is anti-atherogenic and exhibits antiplatelet activity by indirectly down regulating platelet activation receptors. The promising data¹³ requires studies that assess the compliance rate of rivaroxaban among patients as well as the reasons for non-compliance including (but not limited to) side effects and adverse effects. This will ensure a more comprehensive and evidence-based approach for the long and short-term use of Rivaroxaban.

Very scarce literature is present regarding the factors associated with Rivaroxaban among patients. Improved compliance to the use of rivaroxaban for deep venous thrombosis will lead to fewer hospital admissions for complications such as life-threatening pulmonary embolism.

Therefore, in order to develop a more comprehensive and evidence-based approach for the long and short-term use of Rivaroxaban, the present study was undertaken. The objectives of the study were to assess the degree of compliance of patients currently on Rivaroxaban in our population. Furthermore, the study also explored factors associated with non-compliance of Rivaroxaban in patients with deep venous thrombosis.

MATERIALS AND METHODS

An observational longitudinal study was conducted at the Department of Surgery, Aga Khan University & Hospital, Karachi between June 2022 to November 2022. A consecutive, non-probability sampling was employed to recruit participants in the study. The sample size was calculated using OpenEpi software by using the expected proportion of adherence to treatment as 88%,¹⁴ an inflation of 10%, a margin error of 5%, and a confidence level of 95%. A sample size of 180 patients was determined.

Patients with known malignancy with or without chemotherapy, those with a known diagnosis of hypercoagulability disorder or a history of limb trauma leading to deep venous thrombosis were included in the study. Patients who have refused to start rivaroxaban treatment prescribed by vascular surgeons, those with cognitive disabilities, such as dementia, who need to rely on a caregiver for their medical care were excluded.

15 milligrams of Rivaroxaban twice daily for 3 weeks, then 20 milligrams onward was prescribed by a vascular surgeon. Non-adherence was defined as patients who have willingly discontinued the use of rivaroxaban prior to the total duration recommended by the vascular surgeon or patients who missed medications at least twice per week.

Eligible patients were requested to give informed consent. Using a predefined questionnaire, the participants were interviewed at one month and three months of initiating rivaroxaban treatment. Age, gender, indication of use of rivaroxaban and comorbidities were noted. On phone call-up, the medication use, rate of missed doses, self-reported side effects, and different factors of non-adherence to the prescribed treatment were recorded.

The number of patients who were admitted to the hospital for bleeding as a result of anticoagulation therapy was also observed. Patients who were found to be non-compliant with their rivaroxaban prescription were requested to visit the clinic in order to have detailed counseling regarding the importance of their prescription and ways to keep compliant with the prescription.

Data was analyzed using SPSS version 24. Frequency and Percentages were reported for the categorical variables such as indication, comorbidities, medication use, missing dose, side

effects. Mean \pm SD was reported for quantitative variables such as age and duration of anticoagulant therapy. The association between non-adherence and clinical factors were sought using Chi-square test. A p-value of < 0.05 was deemed as the cut-off for statistical significance.

Permission was taken from Ethical Review Committee (ERC) Board of Aga Khan University, Karachi. Participants of the study will be explained the purpose of the study before participation and an informed consent was signed by them. They were reassured that participation is completely voluntary and the participants were ensured that non-participation would not affect their treatment. Identity of the patient was kept confidential and data was not shared with any other party.

RESULTS

A total of 180 patients were recruited with a mean age of 66.3 ± 8.2 years.

Majority (51.6%) were males. The most common indication for rivaroxaban medication was for post-thrombosis patients. 111 (61.6%) patients claimed they missed at least one dose (Table 1).

Table 1: Demographic and clinical characteristics of patients

Parameters	Mean / N (%)
Age in years	66.3 \pm 8.2
Gender	
Male	93 (51.6%)
Female	87 (48.3%)
Duration of Medicine	
A month ago	53 (29.4%)
More than 3 months	92 (51.1%)
More than a year	35 (19.4%)
Indication of Use	
Post thrombectomy	21 (11.6%)
Stroke Prophylaxis	12 (6.6%)
Post-thrombosis	91 (50.55%)
Other	56 (31.11%)
Comorbidities	
Diabetes Mellitus	74 (41.1%)
Hypertension	94 (52.2%)
CAD	29 (16.1%)
Other	10 (5.5%)
Compliance related questions	
How often do you take your medication?	
One a day	127 (70.5%)
Twice a day	21 (11.6%)
Other	32 (17.7%)
Have you ever missed any dose?	
Yes	111 (61.6%)
No	69 (38.3%)
Non-adherence	
Yes	72 (30%)
No	108 (70%)

Out of 180 patients, 100 (55.5%) missed at least one dose during treatment. We reported the self-reported adherence of 70%.

The main reasons are presented in Table 2. Majority revealed that they forget to take medicine or experienced side effects 60 (33.3%). Out of 60 (33.3%) patients who experienced side effects, 10 (5.5%) had bleeding. Of these five patients were hospitalized due to serious adverse events (bleeding per rectal and gastrointestinal).

Table 2: Reasons for non-adherence among patients

Reason for Non-adherence	N (%)
Forgetfulness	78 (43.3%)
Side effects	60 (33.3%)
Affordability	43 (23.8%)
Unavailability in the market	30 (16.6%)
No perceived benefit	12 (6.6%)
Developed Contraindication	9 (5%)

Majority of the patients agreed that use of pill organizers, text messages, and educational brochures would help maintain adherence. Furthermore, patients also suggested that the

prescribing doctor should give more knowledge to ensure better adherence to the medication.

Table 3: Patients' suggestions to improve adherence

Do you think pill organizers, text messages, educational brochures will encourage adherence?	
Yes	134 (74.4%)
No	46 (25.5%)
Do you think physicians should give more knowledge to ensure better adherence to the medication?	
Yes	175 (97.2%)
No	5 (2.7%)

DISCUSSION

A significant percentage of non-adherence among participants was found in our study. One of the primary causes of non-adherence was forgetfulness. However, undesirable side effects like bleeding also made patients less likely to take their medicine as prescribed.

Our study is in accordance with published literature. A study revealed that the global compliance for rivaroxaban was 84.1% and 80.3% after six and one-year post-prescription, respectively. It was also reported that the regular compliance was decreased by 3.5% in 6 months.¹⁵

In contrast to our study, a research by Prins MH assessed the self-reported medication satisfaction and found a higher satisfaction associated with rivaroxaban treatment in comparison to the enoxaparin and vitamin K treatment. Rivaroxaban therapy was observed to be substantially less taxing than enoxaparin/VKA therapy, with significantly stronger therapeutic results.¹⁶ Lana A. Castellucci and colleagues explored the self-reported anticoagulation adherence in a tertiary center anticoagulation clinic. Out of those who participated, 26% were taking DOACs. Of these, 102 (79%) were on rivaroxaban. VTE (72%) and AF (18%) were the two main reasons for prescribing anticoagulation. For patients using DOACs, self-reported anticoagulant adherence was found to be 57.1%. Age, female gender, usage of other oral drugs, and retired job status were predictors of anticoagulant adherence. Age, female gender, and usage of additional oral drugs remained substantially linked with anticoagulant adherence in backward selection multivariate analyses.¹⁷

In line with our study, Speed V et al. reported that out of a total of 1028 participants, 113 (11%) were non-adherent to rivaroxaban at 28 days. Main causes reported for nonadherence at one-month were forgetfulness ($p < .001$), carelessness ($p < .001$) or a shift in daily routine ($p < .001$). The main predictor of excellent adherence was older age (adjusted odds ratio, 1.21; 95% confidence range, 1.06–1.39; 1 = adherent).¹⁸

Medication nonadherence is prevalent in chronic disease. The importance of adherence to anticoagulation therapy has grown in significance in recent years with the advent of short-acting direct oral anticoagulants (DOACs).^{19, 20} It is recommended that the physicians should properly counsel the patients, suggest the use of reminders, narrate the risk profile of the drug, and also inform about the possible complications that could arise if the dose is missed or if the patient is non-compliant to the treatment.

There are some limitations to the current study. Firstly, due to the small sample size and non-randomized sampling technique, the study findings cannot be generalized. Secondly, this was a single-centered study. Thus, to further ascertain our findings, it is recommended that large-scale studies should be undertaken to explore the global adherence to DOACs and the predictors of adherence among patients.

CONCLUSION

Our study revealed a high rate of non-adherence among participants. Forgetfulness was one of the main reasons for non-adherence. However, experiencing adverse effects such as bleeding also discouraged patients to adhere to the medication.

Therefore, it is suggested that patients should be counseled properly for the expected outcomes and side effects. Furthermore, use of pill organizers, text messages, educational brochures should be encouraged by the physicians to increase adherence to Rivaroxaban.

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