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Assessing the link between rivaroxaban concentration and the onset of renal impairment in elderly patients: A retrospective observational study

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ABSTRACT

Background: Rivaroxaban is a widely used anticoagulant, but its impact on renal function, particularly at varying plasma concentrations, remains a critical area of investigation. This study examines the relationship between rivaroxaban concentration and renal impairment in elderly patients. **Aims and Objectives:** The aim of the study was to investigate the relationship between rivaroxaban plasma concentrations and the incidence of renal impairment in elderly patients. **Materials and Methods:** A retrospective observational study was conducted on 100 elderly patients prescribed rivaroxaban for atrial fibrillation or venous thromboembolism prevention. Patients were categorized based on their rivaroxaban plasma concentrations into three groups: Low (<50 ng/mL), medium (between 50 and 200 ng/mL), and high (>200 ng/mL). Renal impairment was characterized as having an estimated glomerular filtration rate <60 mL/min/1.73 m². The analysis of the data consisted of Chi-square testing and multivariable logistic regression, with adjustments made for age, gender, baseline renal function, and treatment indication. **Results:** The incidence of renal impairment escalated with increasing rivaroxaban concentrations, 20%, 40%, and 60% in low, medium, and high concentration groups, respectively. Statistical analysis revealed a significant association between rivaroxaban concentration and renal impairment ($\chi^2 = 10.57$, $P = 0.005$). Patients with high concentrations had 2.8-fold higher odds of developing renal impairment compared to the low concentration group. Cox proportional hazards analysis showed a 2.2 times higher hazard of renal impairment in high versus low concentration groups over 18 months. **Conclusion:** Higher trough plasma concentrations of rivaroxaban are associated with an increased risk of renal impairment in elderly patients. This finding highlights the importance of monitoring rivaroxaban levels to mitigate renal risks.

Key words: Rivaroxaban; Renal impairment; Elderly patients; Anticoagulants; Drug monitoring

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INTRODUCTION

The use of anticoagulant therapy, particularly with newer agents such as rivaroxaban, has become commonplace in managing conditions such as atrial fibrillation and the prevention of venous thromboembolism among elderly patients.[1,2] Rivaroxaban, a direct factor Xa inhibitor, offers the advantage of not requiring regular monitoring of the coagulation cascade, which has been seen as a benefit over traditional anticoagulants such as warfarin.[3,4] However, the relationship between the plasma concentrations of rivaroxaban and its potential renal effects is not fully understood, especially in the elderly who are at increased risk of renal impairment due to age-related decline in kidney function.

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Renal impairment is a significant concern as it can exacerbate the risks associated with anticoagulation, including the risk of bleeding.[5] This concern is particularly acute in the elderly population, where renal function tends to decline with age.[6,7] Rivaroxaban is one of the non-Vitamin K antagonist oral anticoagulants (NOACs) that has been shown to be related with an elevated risk of poor renal outcomes, according to investigations that were conducted in the past.[8,9] Given these risks, understanding the pharmacokinetic behavior of rivaroxaban and its association with renal impairment is crucial for optimizing patient safety and treatment efficacy.

Aims and objectives

The primary aim of this study is to investigate the relationship between rivaroxaban plasma concentrations and the incidence of renal impairment in elderly patients.

Determine if higher rivaroxaban levels correlate with increased rates of renal impairment. Assess the impact of demographic and clinical characteristics, such as age, gender, and baseline kidney function, on renal outcomes. Quantify the risk of renal impairment associated with different rivaroxaban concentrations using logistic regression and Cox proportional hazards analysis. Provide evidence-based recommendations for safer prescribing practices of rivaroxaban in elderly populations at risk of renal dysfunction.

MATERIALS AND METHODS

Study design and setting

This retrospective observational study was carried out at Andhra Medical College in Visakhapatnam, from September 2022 to August 2023. It aimed to assess the effects of various plasma concentrations of rivaroxaban on the occurrence of renal impairment in elderly patients.

Inclusion criteria

The following criteria were included in the study:

Age between 65 and 89 years. Patients were currently prescribed rivaroxaban during the study period. Ongoing treatment with rivaroxaban for either: Atrial fibrillation or prevention of venous thromboembolism.

Exclusion criteria

The following criteria were excluded from the study:

Patients younger than 65 or older than 89 years. Patients not currently receiving rivaroxaban treatment. Presence of end-stage renal disease or dialysis, which could independently affect renal function and the pharmacokinetics of rivaroxaban. Significant liver disease is defined as hepatic impairment that is severe enough to have potential impacts on drug metabolism and excretion. History of allergic reactions or hypersensitivity to rivaroxaban or any of its components. Patients receiving other concurrent anticoagulation therapy, which could confound the effects of rivaroxaban. Participation in any other clinical trials during the study period that might influence the outcome measures of this study.

Data collection

Patient data were gathered from medical records, which encompassed demographic details, clinical features, baseline renal function measured by estimated glomerular filtration rate (eGFR), and trough plasma concentrations of rivaroxaban. Renal function was evaluated using eGFR, with values classified into three categories: <90, between 60 and 89, and <60 mL/min/1.73 m^2.

Categorization of rivaroxaban concentration

Patients were categorized into three groups based on their rivaroxaban trough plasma concentrations:[10] Low (<50 ng/mL), medium (50–200 ng/mL), and high (>200 ng/mL).

Outcome measures

The primary outcome was the incidence of renal impairment, defined as an eGFR below 60 mL/min/1.73 m^2 during the study period.

Statistical analysis

Chi-square tests were used to investigate the relationship between rivaroxaban concentration levels and renal impairment. For the purpose of adjusting for potential confounding factors, such as age, gender, baseline kidney function, and indication for rivaroxaban administration, multivariable logistic regression statistical analysis was utilized. Furthermore, a Cox proportional hazards analysis was carried out to evaluate the risk across time, taking into consideration the time-dependent covariates under consideration.

Ethical considerations

The study was approved by the Institutional Ethics Committee (IEC/AMC/2022/14), Andhra Medical College, Visakhapatnam. To maintain patient anonymity, all of the patient data were anonymized.

RESULTS

Study population

The study evaluated 100 elderly patients who were prescribed rivaroxaban. The mean age of participants was 72.5 years (SD±7.2), ranging from 65 to 89 years. The cohort comprised 52% male (52 patients) and 48% female (48 patients) (Table 1). Clinical characteristics indicated

that 60% (60 patients) were treated for atrial fibrillation and 40% (40 patients) for the prevention of venous thromboembolism. Baseline kidney function measured by eGFR was distributed as follows: >90 mL/min/1.73 m^2 in 20% of patients, 60–89 mL/min/1.73 m^2 in 55%, and <60 mL/min/1.73 m^2 in 25% (Table 2).

Rivaroxaban concentration and renal impairment

Patients were categorized based on trough plasma concentrations of rivaroxaban into low (<50 ng/mL), medium (50–200 ng/mL), and high (>200 ng/mL) concentration groups. These groups comprised 30%, 45%, and 25% of the cohort, respectively (Table 3 and Figure 1). Renal impairment during the study was defined as an eGFR below 60 mL/min/1.73 m^2. The incidence of renal impairment increased with higher rivaroxaban concentrations: 20% in the low, 40% in the medium, and 60% in the high concentration groups, with corresponding confidence intervals of 7.8–38.1%, 26.2–55.3%, and 39.1–78.4%, respectively (Table 4 and Figure 2).

Statistical analysis

A Chi-square test revealed a significant association between rivaroxaban concentration levels and the incidence of renal impairment (χ^2=10.57, df=2, P=0.005), indicating an increased risk with higher concentrations (Table 5). Multivariable logistic regression analysis, adjusted for age, gender, baseline kidney function, and rivaroxaban indication, demonstrated that patients in the high concentration group had an odds ratio (OR) of 2.8 (95% CI: 1.3–6.0, P=0.009) for developing renal impairment compared to those in the low concentration group. The medium versus low concentration comparison yielded an OR of 1.9 (95% CI: 0.8–4.5, P=0.15).

Cox proportional hazards analysis

The Cox proportional hazards model, accounting for time-dependent covariates, showed that the hazard of developing renal impairment was 2.2 times higher in patients with high versus low rivaroxaban concentrations over a median follow-up period of 18 months (HR: 2.2, 95% CI: 1.1–4.3, P=0.024) (Table 6).

DISCUSSION

The findings of the study underscore a dose-dependent relationship between rivaroxaban plasma concentrations and the incidence of renal impairment in elderly patients. This correlation holds even after adjusting for potential confounders such as age, gender, baseline renal function, and indication for rivaroxaban use. Analysis using Chi-square and logistic regression reveals a statistically significant increase in the likelihood of renal impairment with higher doses of rivaroxaban, which is consistent with existing literature suggesting adverse renal outcomes may be linked to higher doses of NOACs.[11,12] In addition, the

Table 1: Demographic characteristics of study population

Characteristic	Total (n=100) (%)
Age (years)	
Mean (SD)	72.5 (±7.2)
Range	65–89
Gender	
Male	52 (52)
Female	48 (48)

SD: Standard deviation

Table 2: Clinical characteristics of study population

Characteristic	Total (n=100) (%)
Indication for rivaroxaban use	
Atrial fibrillation	60 (60)
Venous thromboembolism prevention	40 (40)
Baseline eGFR (mL/min/1.73 m^2)	
>90	20 (20)
60–89	55 (55)
<60	25 (25)

eGFR: Estimated glomerular filtration rate

Table 3: Rivaroxaban concentration levels

Concentration level	Plasma concentration (ng/mL)	Patients (n) (%)
Low	<50	30 (30)
Medium	50–200	45 (45)
High	>200	25 (25)

Table 4: Incidence of renal impairment by rivaroxaban concentration

Concentration level	Patients with renal impairment	Percentage	95% confidence interval (%)
Low	6	20	7.8–38.1
Medium	18	40	26.2–55.3
High	15	60	39.1–78.4

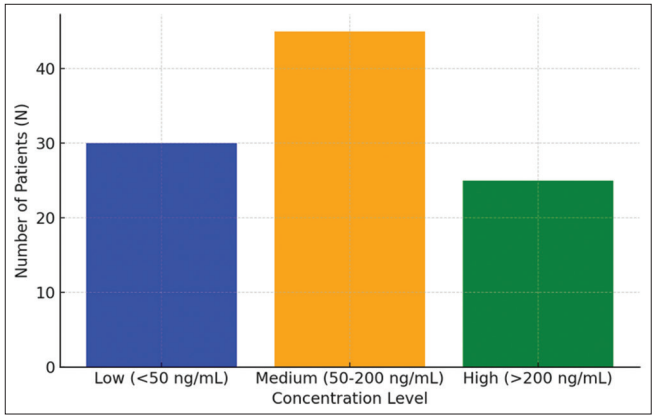

Figure 1: Rivaroxaban plasma concentration levels

Table 5: Statistical analysis results

Analysis type	Comparison	Result	95% CI	P-value
Chi-square test	Association of concentration and renal impairment	χ^2=10.57	df=2	0.005
Logistic regression	High versus low concentration	OR=2.8	1.3–6.0	0.009
Logistic regression	Medium versus low concentration	OR=1.9	0.8–4.5	0.15

OR: Odds ratio, CI: Confidence intervals

Table 6: Model results from Cox proportional hazards analysis

Variable	Hazard ratio	95% CI	P-value
High versus low concentration	2.2	1.1–4.3	0.024

CI: Confidence intervals

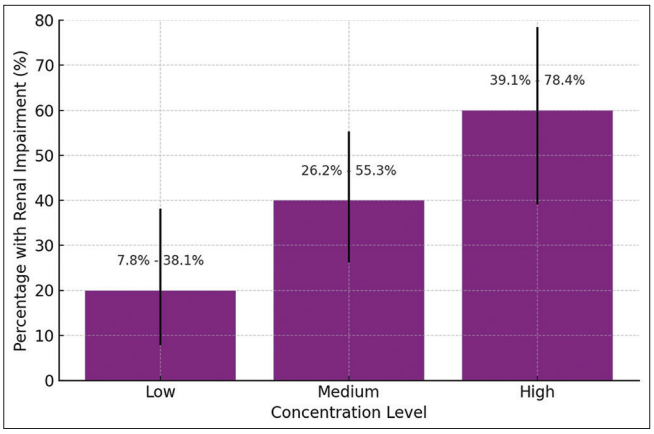

Figure 2: Incidence of renal impairment by rivaroxaban concentration

Cox proportional hazards model employed in our study further supports the hypothesis that prolonged exposure to higher drug concentrations exacerbates renal vulnerability.

Comparative studies have also indicated a general risk of renal complications associated with NOACs, although many did not specify risk levels according to different drug concentrations. By demonstrating a concentration-dependent risk, our study adds precise data that could help shape more targeted dosing guidelines and monitoring protocols, enhancing patient safety. These findings align with those presented by Ravenstijn et al.,[13] Sin et al.,[14] Byon et al.,[15] and De Vriese et al.,[16] which also discussed the renal risks associated with rivaroxaban in specific patient populations.

Clinical implications

The data underscores the necessity for careful rivaroxaban dosing, particularly in elderly patients who are more susceptible to renal impairment due to age-related physiological changes. This study advocates for the potential advantages of periodic monitoring of rivaroxaban plasma levels, which could enable clinicians to tailor doses more effectively and minimize renal risks. Implementing such monitoring could help balance the benefits of anticoagulation with the associated renal risks, leading to better overall patient outcomes.

Limitations of the study

The retrospective nature of this study limits our ability to definitively establish causality between rivaroxaban concentrations and renal outcomes. Moreover, the sample size, while sufficient for initial analysis, may not fully represent the variability and potential outliers that could be encountered in a broader patient population. These limitations suggest the need for a cautious interpretation of the results.

CONCLUSION

This study highlights a significant correlation between higher trough plasma concentrations of rivaroxaban and increased rates of renal impairment among elderly patients. Demonstrated through robust statistical analyses, the findings reveal a dose-dependent risk, reinforcing the need for cautious rivaroxaban dosing in the elderly. The study advocates for the implementation of periodic monitoring of rivaroxaban plasma levels to tailor dosing and reduce renal risk. While highlighting the benefits of proactive monitoring, the findings call for further research to refine treatment protocols, ensuring the balance between anticoagulation efficacy and renal safety in this vulnerable population.

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