International Normalized Ratio Is Significantly Elevated With Rivaroxaban and Apixaban Drug Therapies: A Retrospective Study

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ABSTRACT

Purpose: Direct factor Xa inhibitors such as rivaroxaban or apixaban may prolong prothrombin time (PT) and elevate international normalized ratio (INR). However, these tests are not reliable for assessing the anticoagulation effects of these agents. PT assay sensitivity is relatively weak at therapeutic drug concentrations and is subjected to significant variations depending on the reagent used. Conversion of PT to INR may even increase the variability. We conducted a retrospective cross-sectional study aiming to assess the prevalence and extent of INR elevation in hospitalized patients receiving rivaroxaban or apixaban as part of their home medications and to find out whether other existing factors could elevate INR apart from the drug entity itself.

Methods: The data collected from 218 hospitalized patients' charts included PT and INR taken on admission, patients' characteristics, laboratory results, other medications regularly used, and coexisting clinical conditions.

Findings: No statistically significant association between INR elevation and the parameters examined was found in our study. INR was significantly elevated in both drug groups ($P < 0.001$), with 84.2% of rivaroxaban patients and 78.3% of apixaban patients presenting with INR levels above the higher limit of the normal range. Furthermore, INR was significantly higher in the rivaroxaban group than in the apixaban group ($P < 0.001$).

Implications: Both of the reviewed drugs significantly elevated INR. Moreover, rivaroxaban elevates INR significantly more than apixaban, and there are apparently no other factors affecting INR but the drugs themselves. Larger prospective studies are needed to confirm and clarify the clinical significance of these results. (*Clin Ther*. 2017;39:1003–1010)

Key words: anticoagulants, apixaban, direct anti-factor Xa inhibitors, DOACs, INR elevation, rivaroxaban.

INTRODUCTION

Direct oral anticoagulants (DOACs) have been broadly integrated into clinical practice as effective and tolerable alternatives to traditional vitamin K antagonists (VKAs) for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism. Their rapid emergence has prompted clinicians to abandon their current routine clinical practice and to adopt new approaches to meet the drugs' unique and different treatment strategies. Monitoring their anticoagulant effect is one of the most important issues to be addressed.[1]

Prothrombin time (PT), a commonly used assay in the clinical setting, is the time in seconds for plasma to coagulate after the addition of calcium and thromboplastin, an activator of the extrinsic coagulation pathway, to citrated plasma. PT is most often used to

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monitor warfarin because of its inhibition of the vitamin K–dependent factors II, VII, IX, and X. Inhibitors or deficiencies of these coagulation factors prolong PT. One of the disadvantages of the PT assay is the varying sensitivities of the available thromboplastin agents to the reduction in coagulation factors. To correct for the variability of the thromboplastin reagent used, PT is converted to an international normalized ratio (INR) through a mathematical calculation by using the manufacturer's international sensitivity index (ISI). The ISI reflects the responsiveness of a given thromboplastin to the reduction of these coagulation factors, compared with the primary World Health Organization international reference preparations, so that the more responsive the reagent, the lower the ISI value. Once calculated, the INR can be evaluated without regard to the thromboplastin reagent used in the PT assay.

Because VKA therapy requires regular coagulation monitoring of the PT/INR as result of of their narrow therapeutic window, the use of the DOACs alleviates the need for routine laboratory monitoring for their more predictable pharmacokinetic and pharmacodynamic profiles.[2]

Direct factor Xa inhibitors such as rivaroxaban or apixaban may prolong PT[1,2] and elevate INR in a concentration-dependent, incremental manner through their inhibition of free and bound factor Xa.[3–5] In contrast to the VKAs, this PT prolongation is short-lived and changes during the course of the day. For example, rivaroxaban has no significant influence on PT 24 hours after tablet intake.[6,7] Nevertheless, PT assay sensitivity is relatively weak at therapeutic drug concentrations and is subjected to significant variations depending on the reagent used.[1,2,6] Furthermore, PT is not specific and can be influenced by many other factors (eg, hepatic impairment, cancer, vitamin K deficiency).[8] The limited sensitivity of the PT to factor Xa inhibitory activity, coupled with the variability in the sensitivity of different thromboplastin reagents to factor Xa inhibitors, may limit the utility of the PT as a method for quantitative assessment of the anticoagulant effect of oral factor Xa inhibitors.[9] Conversion of PT to INR, which is calibrated for use with VKA only, does not correct for the variation and even increases the variability. Therefore, elevated INR that is frequently observed in patients treated with rivaroxaban and apixaban is not a viable option to assess efficacy and tolerability of factor Xa inhibitors.[10] Standardized anti-factor Xa chromogenic assay kits are now commercially available for quantitative measurements of rivaroxaban and apixaban exposure.[1,5,6,11,12]

Currently, a PT assay is still used in an emergency or urgent clinical scenario to determine whether an anticoagulation effect caused by direct factor Xa inhibitors is present, absent, or at supratherapeutic levels.[9] Documented reports exist about rivaroxaban-induced PT prolongation and INR elevation in real-life patient cohorts.[3,4] However, the impact of apixaban on PT assay was only tested in vitro on blood samples drawn from healthy individuals, displaying a low sensitivity to a wide range of reagents.[13,14]

Attempts to interpret INR tests may be misleading, bringing to incorrect clinical decisions and life-threatening discontinuation of essential treatments with these medications. Furthermore, real-life data about these drugs effect on INR is scarce. We therefore conducted a retrospective cross-sectional study aiming to assess the prevalence and extent of INR elevation in hospitalized patients receiving rivaroxaban or apixaban as part of their home medications and to find out whether other existing factors could elevate INR apart from the drug entity itself.

PATIENTS AND METHODS

The study was approved by the local institutional review board. This retrospective cross-sectional study was conducted at Assaf Harofeh Medical Center, one of Israel's largest tertiary medical centers, with >800 acute care beds. It serves a population of $>500{,}000$ in central Israel. The hospital provides major services, including emergency, intensive care, general medical, surgical, cardiac, pediatric, neonatal, gynecologic, and obstetric services.

Participants

Participants were patients older than 18 years, admitted to our institution from January to July 2015, who had been regularly treated with rivaroxaban or apixaban before admission and underwent INR testing during their first 24 hours of admission.

Variables

Variables were patient's demographic data (age, sex); hematologic tests, including white blood count,

Table I. Patient characteristics on admission and comparison between the rivaroxaban and apixaban groups.

Characteristic	Study Population (n = 218)	Rivaroxaban Group (n = 158)	Apixaban Group (n = 60)	*P* Value*
Age, median (IQR), y	79.1 (72.4–85.2)	78.8 (71.2–85.3)	80.1 (75.4–85)	0.439
Male sex, no. (%)	108 (49.5)	83 (52.5)	25 (41.7)	0.152
BMI, median (IQR), kg/m^2	27.5 (24.6–31.6)	27.3 (24.6–31.7)	28.3 (25–31.5)	0.488
GFR, median (IQR), mL/min	54 (42–71.3)	55 (43–71.7)	52 (38.5–69)	0.305
International normalized ratio	1.6 (1.3–2.2)	1.7 (1.3–2.5)	1.4 (1.2–1.6)	<0.001
Prothrombin time, median (IQR), sec	20.7 (17.6–27.2)	22.3 (18–30)	19.1 (16.6–21)	<0.001
White blood cells, median (IQR), K/μL	9 (7.3–11.4)	9 (7.5–11.1)	8.8 (7–12.8)	0.506
Hemoglobin, mean [SD], g/dL	11.5 [2.2]	11.6 [2.2]	11.1 [2.2]	0.184
Platelets, median (IQR), K/μL	215.5 (169.5–257.7)	218 (172.5–258.5)	206 (163–257)	0.326
Bilirubin, median (IQR), mg/dL	0.5 (0.3–0.7)	0.52 (0.35–0.73)	0.6 (0.4–0.8)	0.274
Albumin, median (IQR), g/L	37 (33–39)	37 (34–39.2)	35 (32–38)	0.017
Alanine aminotransferase, median (IQR), U/L	17 (12–26)	17 (12–23.7)	16 (12–39)	0.524
Aspartate aminotransferase, median (IQR), U/L	21 (16–32)	21 (16–30.5)	22 (17–39)	0.203
Indication for anticoagulant, no. (%)				
Atrial fibrillation	214 (98.2)	155 (98.1)	59 (98.3)	>0.99
Deep vein thrombosis	4 (1.8)	3 (2)	1 (1.7)	>0.99
Pulmonary embolism	2 (0.9)	1 (0.7)	1 (1.7)	0.482
Previous medication use, no. (%)				
Statins	130 (59.6)	94 (59.5)	36 (60)	0.946
Angiotensin-converting enzyme inhibitor	63 (28.9)	44 (27.8)	19 (31.7)	0.579
Angiotensin II receptor blockers	57 (26.1)	38 (24.1)	19 (31.7)	0.253
Calcium channel blockers	58 (26.6)	44 (27.8)	14 (23.3)	0.5
α-Blockers	51 (23.4)	33 (20.9)	18 (30)	0.156
β-Blockers	135 (61.9)	93 (58.9)	42 (70)	0.13
Antiarrhythmic agent	65 (29.8)	47 (29.7)	18 (30)	0.971
Diuretic agent	126 (57.8)	88 (55.7)	38 (63.3)	0.308
Aspirin	47 (21.6)	36 (22.8)	11 (18.3)	0.475
Clopidogrel	15 (6.9)	11 (7)	4 (6.7)	>0.99
Psychotropic drugs	82 (37.6)	64 (40.5)	18 (30)	0.153
Proton pump inhibitors	100 (45.9)	66 (41.8)	34 (56.7)	0.049
Antibiotics	19 (8.7)	8 (5.1)	11 (18.3)	0.002
Non-insulin antidiabetic drugs, total	67 (30.7)	50 (31.6)	17 (28.3)	0.636
Comorbidity, no. (%)				
Cardiovascular diseases	197 (90.4)	143 (90.5)	54 (90)	0.91
Essential hypertension	170 (78)	124 (78.5)	46 (76.7)	0.773
Hyperlipidemia	120 (55)	91 (57.6)	29 (48.3)	0.22
Chronic kidney disease	31 (14.2)	18 (11.4)	13 (21.7)	0.052

(continued)

Table I. (continued).

Characteristic	Study Population (n = 218)	Rivaroxaban Group (n = 158)	Apixaban Group (n = 60)	*P* Value*
Infections	30 (13.7)	17 (10.7)	13 (21.6)	0.012
Diabetes mellitus	109 (50)	78 (49.4)	31 (51.7)	0.762
Cerebrovascular diseases	16 (7.3)	14 (8.9)	2 (3.3)	0.247

BMI = body mass index; GFR = glomerular filtration rate; IQR = interquartile range.
*P value refers to the differences between rivaroxaban and apixaban patients.

hemoglobin, platelets, INR, and PT; biochemical tests, including liver enzymes, bilirubin, and glomerular filtration rate (GFR) calculated with the Modification of Diet in Renal Disease formula; body mass index; indication for anticoagulant use; other medications used on admission; and comorbidities.

Data Sources

The data were collected mainly from the patient's electronic medical records. With missing data we were also assisted by the database provided by the hematology and biochemistry laboratories. The PT/INR was determined using coagulation analyzer ACL TOP-500 (Instrumentation Laboratory, Bedford, Massachusetts). The reagent used was PT-Fibrinogen HS PLUS – 0008469810 (Instrumentation Laboratory).

Study Size

To identify a difference of 0.5 in INR between patients receiving rivaroxaban compared with apixaban with a significance level of 5% and 80% power, 64 patients were needed in each group (SD = 1). When we assumed a ratio of 2:1 (rivaroxaban/apixabin), we needed 96 patients in the rivaroxaban group and 48 in the apixaban group.

Statistical Analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test and continuous variables by independent samples *t* test, the Mann-Whitney test, or Kruskal-Wallis test. Correlation between continuous variables was evaluated using Spearman's rank-order correlation. The association between rivaroxaban and apixaban with INR adjusted for potential confounders was assessed by multivariate linear regression. In the regression analysis, INR values were natural log-transformed to achieve normality. Age, sex, indication for anticoagulant, and variables with $P < 0.1$ in the univariate analysis were included in the multivariate analysis. The linear regression was evaluated to meet the regression assumptions. One-sample Wilcoxon signed rank test was used to compare INR values with the upper limit of the normal range (1.2). A two-tailed $P < 0.05$ was considered statistically significant. The analyses were performed with SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, New York).

RESULTS

Two hundred eighteen patients were included in the study. Patient characteristics and comparison between the rivaroxaban and apixaban groups are presented in Table I. We identified 50 drugs and drug groups concurrently used with rivaroxaban or apixaban, and 27 coexisting clinical conditions. The characteristics presented in Tables I and II were selected because of their high frequency of use or occurrence.

Comparison of patient characteristics on admission between the rivaroxaban and apixaban groups has not revealed any significant differences for most characteristics. However, several factors indicated substantial differences between the 2 groups. Analyzing this data further eliminated any association with INR levels (Table I). Furthermore, no statistically significant association between INR elevation and the parameters examined was observed (Table II), including age ($r = 0.061$, $P = 0.369$) and sex (male: median, 1.61 [interquartile range (IQR), 1.33–2.29]; female: median, 1.54 [IQR, 1.26–2.16]; $P = 0.363$). In multivariate linear regression analysis, patients treated with apixaban had 25% lower INR than patients treated with rivaroxaban. Moreover, aspirin therapy

Table II. Association between INR and patient characteristics.

Characteristic	*r*	Yes	No	*P* Value
Continuous variable				
BMI, kg/m^2	0.028			0.698
GFR, mL/min	0.04			0.554
White blood cells, K/μL	0.026			0.702
Albumin, g/L	0.053			0.47
Alanine aminotransferase, U/L	0.005			0.949
Aspartate aminotransferase, U/L	0.019			0.788
Categorical variable, median (IQR), INR				
Indication for anticoagulant				
Atrial fibrillation		1.59 (1.29–2.22)	1.27 (1.09–1.69)	0.158
Deep vein thrombosis		1.27 (1.09–1.69)	1.59 (1.29–2.22)	0.163
Pulmonary embolism		1.27 (1.21–1.83)	1.59 (1.29–2.22)	0.213
Previous medication use				
Statins		1.59 (1.29–2.21)	1.58 (1.3–2.2)	0.906
Angiotensin-converting enzyme inhibitor		1.59 (1.24–21.6)	1.59 (1.3–2.33)	0.732
Angiotensin II receptor blockers		1.38 (1.25–2.05)	1.65 (1.31–2.22)	0.055
Calcium channel blockers		1.48 (1.29–2.2)	1.61 (1.29–2.21)	0.499
α-Blockers		1.64 (1.39–2.14)	1.59 (1.28–2.22)	0.587
β-Blockers		1.58 (1.29–2.14)	1.61 (1.3–2.44)	0.624
Antiarrhythmic agents		1.53 (1.21–2.41)	1.59 (1.32–2.15)	0.729
Diuretic agents		1.56 (1.31–2.21)	1.66 (1.24–2.21)	0.847
Aspirin		1.44 (1.29–1.7)	1.65 (1.3–2.33)	0.012*
Clopidogrel		1.49 (1.33–2.14)	1.61 (1.29–2.22)	0.571
Psychotropic drugs		1.56 (1.28–2.26)	1.6 (1.31–2.2)	0.840
Proton pump inhibitors		1.58 (1.29 –2.22)	1.6 (1.28–2.21)	0.936
Antibiotics		1.47 (1.22 –1.99)	1.59 (1.29–2.22)	0.545
Non-insulin antidiabetic drugs, total		1.59 (1.33 –1.91)	1.6 (1.29–2.33)	0.642
Comorbidity				
Cardiovascular diseases		1.59 (1.3–2.22)	1.6 (1.2–2)	0.429
Essential hypertension		1.6 (1.3–2.22)	1.49 (1.22–2.06)	0.230
Hyperlipidemia		1.6 (1.31–2.21)	1.58 (1.27–2.17)	0.338
Chronic kidney disease		1.52 (1.31–1.97)	1.61 (1.29–2.22)	0.565
Infections		1.48 (1.27–1.87)	1.61 (1.29–2.22)	0.256
Diabetes mellitus		1.56 (1.31–1.98)	1.61 (1.27–2.32)	0.888
Cerebrovascular diseases		1.6 (1.06–2)	1.59 (1.3–2.23)	0.248

BMI = body mass index; GFR = glomerular filtration rate; INR = international normalized ratio; IQR = interquartile ratio.
*Lower INR values were observed in patients receiving aspirin.

was associated with 14% lower INR (Table III). INR was significantly elevated in both drug groups ($P < 0.001$), with 84.2% (133 patients) of the rivaroxaban group and 78.3% (47 patients) of the apixaban group presenting with INR levels above the higher limit of the normal range. INR was significantly higher in the rivaroxaban group (median, 1.7 [IQR, 1.3–2.5]) than in the apixaban group (median, 1.4 [IQR, 1.2–1.6]; $P < 0.001$) (Figure 1 represents INR values in patients treated with rivaroxaban versus patients treated

Table III. Multivariate linear regression of the association with INR (β values after back transformation).

Characteristic	β	95% CI	*P* Value
Age	1.004	0.999–1010	0.07
Male sex	1.029	0.928–1.140	0.58
DVT	0.857	0.592–1.239	0.401
ARBs	0.911	0.814–1.020	0.108
Aspirin	0.856	0.760–0.965	0.011
Apixaban	0.749	0.670–0.837	<0.001

ARB = angiotensin II receptor blocker; DVT = deep vein thrombosis, INR = international normalized ratio.

with apixaban). No association was found between rivaroxaban doses (10, 15, 20 mg) or apixaban doses (2.5, 5 mg) and INR levels ($P = 0.622$, $P = 0.13$, respectively). No bleeding events were reported.

DISCUSSION

The predicted pharmacologic profile of the direct factor Xa inhibitors allows the administration of the drug at fixed doses without the need for routine laboratory monitoring or dose adjustments. However, the use of a reliable assay to assess anti-factor Xa activity may be needed in rare situations, such as serious bleeding and thrombotic events, need for urgent surgery, or in special clinical situations such as patients who present with renal or hepatic insufficiency, potential drug–drug interactions, suspected overdosing, or assessment of compliance.[15] In addition to the valuable knowledge of the extent of anticoagulant effect there is a need for clinicians to know whether coagulation assays are influenced by rivaroxaban/apixaban use. Measurement of the PT and activated partial thromboplastin time and in some hospitals the fibrinogen levels is a routine procedure in the emergency department and when patients are hospitalized. Because these tests are affected by factor Xa inhibitors, "abnormal results" may be misinterpreted by nonexpert clinicians. For example, in a patient with sepsis, prolongation of the PT and activated partial thromboplastin time may be caused by a factor Xa inhibitor rather than the sepsis itself. All acute care clinicians should acquire knowledge of how routine coagulation tests are affected, because many patients having a "coagulation screen" will be taking these drugs. The biggest educational challenge is not going to be with clinicians who prescribe and manage anticoagulant therapy but with the many clinicians who are not routinely involved in anticoagulant care but who will nevertheless encounter an increasing number of patients incidentally taking these drugs. Furthermore, although the stronger correlation between levels of rivaroxaban and apixaban and factor Xa activity in a chromogenic assay favors its use, the use of these assays is currently limited because of availability and cost issues, whereas the PT assay is readily available and easily performed in most laboratories.[16] These drugs indicate a concentration-dependent PT prolongation, but because of the assays' weak sensitivity and a wide reagent-dependent variability, this test is not reliable to quantitatively evaluate factor Xa inhibitory activity. Furthermore, the time that the sample is drawn relative to the most recent dose of a DOAC significantly affects its measured effect, in contrast to VKAs, in which the PT/INR reflects the cumulative effect of multiple recent doses.

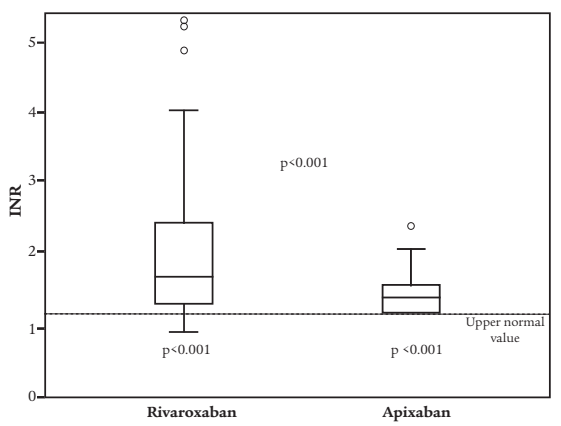

Figure 1. International normalized ratio (INR) values in patients treated with rivaroxaban versus patients treated with apixaban, represented by box-and-whisker plot, n = 218.

Compared with previous studies that assessed the pharmacodynamics of these drugs on healthy participants,[13,14,17] this study found elevated INR in a real hospitalized elderly patient cohort treated with either rivaroxaban or apixaban mainly for atrial fibrillation. Furthermore, our study found marked differences

between apixaban and rivaroxaban in relation to the prevalence and extent of the INR elevation.

The number of patients with infections was higher in the apixaban group. However, these were mild respiratory infections that presumably did not affect the INR results. In relation to adjusting the appropriate dose considering patient specific characteristics, data of the patients participating in our study were reviewed to reassure appropriate dose adjustment. According to the prescribing information for rivaroxaban and apixaban (for stroke prevention in nonvalvular atrial fibrillation) dose adjustment for rivaroxaban is recommended when the estimated GFR ranges between 30 and 49 mL/min and for apixaban if creatinine clearance is 15 to 29 mL/min or if two of the following criteria are met: age $\geq$80 years, weight $\leq$60 kg, serum creatinine $\geq$1.5 mg/dL. All of the 65 patients in the rivaroxaban group, who had GFR 30 to 49 mL/min received the lower dose (15 mg once daily for rivaroxaban). The age of 7 patients receiving the standard dose of apixaban (5 mg twice daily for apixaban) exceeded 80 years. Their creatinine clearance ranged between 57 and 82 mL/min, and none of them weighted $<$60 kg.

There are two proposed explanations for the diverse elevated INR results between the two drugs. First, the PT assay has relatively lower sensitivity to apixaban than to rivaroxaban in therapeutic drug concentrations.[1,18] Second, the diversity may also derive from the difference of the drugs' daily dosage regimen. Rivaroxaban is administered once daily (for most of its indications), whereas apixaban is administered twice daily. This once daily administration of rivaroxaban exhibits higher fluctuations in the drug's plasma concentration,[19] suggesting correlation with higher INR levels.

The findings of our study support the accumulated current knowledge that direct factor Xa inhibitors elevate INR as part of their pharmacodynamic activity and that INR is not a viable option to assess their effectiveness and safety profile, because it is calibrated for use with VKA only.[6] The finding that no bleeding event was reported in our study correlates with our comprehension that interpretation of INR levels during treatment with direct factor Xa inhibitors may bring clinicians to incorrect clinical decisions.

Our study has limitations. It was a retrospective study; therefore, we were unable to trace the actual drug administration time in relation to blood sampling, which might have affected the data on INR elevation. Baseline INR/PT was not available in our patient cohort. Patients participating in our study were admitted to the emergency department without baseline PT/INR, because these tests are not routinely performed in the community on patients taking direct anti-factor Xa inhibitors. Another limitation is that possible drug–drug interactions and their possible impact on INR levels were not evaluated in each patient in our study. However, implementation of this evaluation should be handled with care because the information on drug interactions with DOACs is incomplete.[20]

CONCLUSIONS

Both of the reviewed drugs significantly elevated INR. Moreover, rivaroxaban elevated INR significantly more than apixaban, and there were apparently no other factors affecting INR but the drugs themselves. However, larger prospective studies are needed to confirm our results to clarify their clinical significance.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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