Research Article

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The Value of Testing DOACs Anti-Xa Activity and its Relation to Laboratory Findings and Patient-Specific Clinical Parameters

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Abstract

Background: DOACs are well-known to have predictable pharmacokinetic and pharmacodynamic responses and do not require monitoring. However, some of the factors that have been shown in the literature to affect their activity include kidney function, weight, and age.

Objective: To assess the correlation of anti-factor Xa activity with different patient-specific clinical parameters.

Methods: This is a retrospective, single center study. All patients who used apixaban or rivaroxaban with anti-factor Xa activity measured at a certain point were included in the study. The primary endpoint is to measure the correlation of different patient-specific data, including age, body mass index (BMI), creatinine clearance (CrCl), glomerular filtration rate (GFR), to anti-factor Xa activity.

Results: Eighty samples were screened and reviewed. Anti-Xa activity had a weak negative correlation with age (r= -0.161, p= 0.1531) and BMI (r= -0.093, p= 0.4090), and a weak positive correlation with GFR (r= 0.142, p= 0.2061) and CrCl (r= 0.180, p= 0.1088). Anti-Xa activity had a weak positive correlation with thrombosis (r= 0.05, p= 0.8296) and a semi strong positive correlation with bleeding (r= 0.733, p= 0.4090). Despite showing a weak positive correlation, the correlation between the international normalized ratio (INR) and anti-Xa activity was statistically significant (r= 0.249, p= 0.027).

Conclusion: Clinical parameters such as age, GFR, CrCl, BMI, and body weight as well as the incidence of thrombosis didn't show a strong or statistically significant correlation with anti-Xa activity level. More robust studies are needed to evaluate this correlation and help guide clinicians to making clinical decisions.

Introduction

The Direct Oral Anticoagulants (DOACs) are the newest oral anticoagulants available, and they consist of the direct thrombin inhibitors and the factor Xa inhibitors. Dabigatran, a direct thrombin inhibitor, was the first DOAC to be approved in 2010. Prior to its approval, the only oral anticoagulant that was available was warfarin. Its inhibition of thrombin leads to a decrease in the formation of fibrin and reduces the stimulation of platelet aggregation, thus preventing the formation of thrombi. The other widely used oral anticoagulants which are called factor Xa inhibitors, and they exert their effect by blocking the action of factor Xa in the blood and in the preexisting clots selectively and reversibly, therefore preventing further clot formation. The most commonly used factor Xa inhibitors are apixaban and Rivaroxaban[1,2]. These medications are used for different indications, which include the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); reducing the risk of recurrent DVT and PE following initial therapy, and reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF)[3,4]. Even though it is well-known that DOACs result in predictable anticoagulation with effective fixed doses and no biochemical monitoring is currently recommended, high inter-individual variability in drug blood levels has been shown with all DOACs.

DOACs monitoring is less well established when compared with Heparin and Warfarin. The European Heart Rhythm Association (EHRA) provided a guidance regarding the use of aPTT and prothrombin time (PT) for the qualitative assessment of the presence of certain DOACs without specific ranges. Quantitative tests such as plasma drug concentration and anti-factor Xa level are capable of measuring the level of DOACs in the blood. However, since there are no recommendations regarding the indications for monitoring the patients or the appropriateness of the tests, they do not have clinical roles currently and there are no specific recommendations regarding when to use them for patients receiving DOACs[5].

The plasma concentrations of DOACs were shown to correlate with either bleeding risk, or thrombotic outcomes, which necessitates the monitoring of these medications. Monitoring might be more clinically relevant among patients who might have different factors that can affect the pharmacokinetics of the drug (e.g., renal function, weight, and age). Limited data are available to correlate results of these plasma concentrations with clinical outcomes. Correlation of the DOACs' pharmacokinetics to the change in the hemostasis factors could also help in identifying patients who are at risk of developing adverse events to the medications or who would benefit from the medications. However, there is no data correlating anti-Xa activity during

assumed maximum and minimum concentrations of DOACs with regards to patient-specific laboratory values and clinical outcomes.

The objective of this study is to assess the correlation of anti-factor Xa activity with different patient-specific clinical parameters and DOACs doses.

Method
Design:
This is a retrospective, single center study which will be conducted in a tertiary care hospital in Riyadh, Saudi Arabia. All patients who took apixaban or rivaroxaban with anti-factor Xa activity measured at a certain point with chromogenic anti-Xa assay in the inpatient or outpatient settings were included in the study from December 2017 (when the testing became available in the hospital) until March 2021. The study was approved by the research advisory council (RAC) with the number 2211222.

Data collection:
The data was collected from the Integrated Clinical Information System (ICIS) in the hospital. For all the patients identified to be included in the study, their demographic data including age, weight, height, BMI, GFR, past medical history and past surgical history were collected for analysis. The data collected for the samples included which of the two DOACs was used, what indications it was used for, in addition to the indication of testing for the anti-Xa level. Furthermore, data regarding the initial dose that was used and change in the dosing were collected. Anti-Xa activity levels were collected for all patients as well as their timing. Other lab values which were collected included the anti-Xa activity level, hemostasis assays including INR, PT, fibrinogen, aPTT, platelets, Hgb, and D-dimer.

Patient selection:
Patients taking a DOAC with anti-factor Xa activity during the inclusion time period were included, and patients taking a DOAC without anti-factor Xa activity levels were excluded.

Primary and secondary endpoints:
The primary endpoint is to measure the correlation and predictability of different patient-specific data, including age, body mass index (BMI), glomerular filtration rate (GFR), to anti-factor Xa activity and DOACs dose at peak or trough time. The first secondary endpoint is to measure the correlation between anti-factor Xa activity with the development of arterial and venous thromboembolism within 1 year. Arterial thrombosis is defined as developing coronary artery thrombus, pulmonary artery thrombus, or stroke. Venous thrombosis is defined as the development of deep vein thrombosis (DVT), cerebral venous thrombosis, or femoral vein thrombosis. Another secondary endpoint is to measure the correlation between anti-factor Xa activity with the development of major (including life threatening) and minor bleeding within three months. Major bleeding is defined as a decrease in the hemoglobin level of at least 20 g per liter, transfusing at least 2 units of blood, or symptomatic bleeding in a critical life organ[6]. Life threatening bleeding is considered a subcategory of major bleeding, which is defined as fatal, symptomatic intracranial bleeding, bleeding with a decrease in hemoglobin level of at least 50 g per liter, or bleeding which requires the transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleedings are considered minor bleedings.

Moreover, we aimed at identifying the most common indications for testing and measuring the correlation between the results and clinical outcomes.

Statistical analysis:
For this retrospective study, all statistical analyses of data were done using the SAS software package, version 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics for continuous variables will be reported as mean ± standard deviation and categorical variables were summarized as frequencies and percentages. The median and interquartile range (IQR) will be used when deemed necessary. Correlation test will be performed using Pearson/Spearman Correlation Coefficient (r). The level of significance is set at p-value < 0.05. All patients who have been on DOACs with anti-factor Xa activity results at a certain point during the treatment period will be included, therefore, the sample size was imposed based on the number of patients who had the tests done during the specified period from December 2017 until March 2021, which is estimated to be 80 patients.

Results
A total of 80 samples during the predefined study period were screened and reviewed. Baseline characteristics are shown in table 1. Forty-one of the 80 samples were for male patients with a median age of 62.5. Forty-two (52.5%) of the samples were taken for patients who were on Apixaban and 38 samples for patients on Rivaroxaban. In addition to being on DOAC, 13 (16.25%) patients were on heparin and 13 (16.25%) patients were on aspirin.

Primary End Point:
Age has shown to have a weak negative correlation with age (r= -0.161, p= 0.1531) and BMI (r= -0.093, p= 0.4090), and a weak positive correlation with GFR (r= 0.142, p= 0.2061) and CrCl (r= 0.180, p= 0.1088). None of the clinical parameters tested had shown significant correlations with anti-factor Xa activity (table 2) (figure 1).

Secondary End Points:
Anti-factor Xa activity has shown to have a weak positive correlation with thrombosis (r= 0.05, p= 0.8296) and a moderate positive correlation with bleeding (r= 0.733, p= 0.4090) (table 3). Among all the coagulation assays, only INR has shown a statistically significant (r= 0.249) (p= 0.027), while all the other assays were not shown to have a significant correlation with the anti-Xa activity level (appendix B). The questionable absorptive capacity of oral anticoagulants due to bowel resection was found to be as the indication for testing among 23.25% of the samples, followed by renal dysfunction in 15.11% of the samples. Minor and major bleeding were the indications for 13.95% and 11.62% respectively, while an elevation in the INR was the indication for 8.13%. Fifteen (18.75%) of the samples were shown to be out of the anti-Xa normal range, four (5%) of them had high levels while 11 (13.75%) had low levels. In the patients who had high levels, two (2.5%) had a change of the dose being administered after that and 2 (2.5%) had no change. For the patients who had low levels, five (6.25%) had their doses changed and 6 (7.5%) had no change (appendix C). With apixaban 2.5 mg dosing, the testing was done in 5 (6.25%) patients who had low anti-Xa activity levels. The indications of testing in those patients were minor bleeding (3), major bleeding (1), and renal dysfunction (1). In case of 5 mg dosing, the testing was done in 4 patients with high anti-Xa activity levels and 6

patients with low anti-Xa activity levels. For the 4 patients who had high levels, the indications of testing were minor bleeding (1), major bleeding (1), renal dysfunction (1), and in one case, the indication was not documented (1). For the 6 patients who had low levels, the indications of testing were venous thrombosis and renal dysfunction (4), major bleeding (1), and questionable absorptive capacity of oral anticoagulants (1) (appendix D). When adjusting for the correlation of the different clinical parameters tested for in the primary outcome based on the indication, none of the clinical parameters has shown a statistically significant correlation with anti-Xa activity levels (appendix E). The average time of sample collection was 2.78 hr before the administration of the next dose in 19 trough levels, and 3.84 hr after the administration of the last dose for 41 peak levels. The rest of the samples were random.

Discussion

General finding: Despite DOACs being introduced as medications which don't need monitoring, clinicians have been observing a variation in the response to DOACs among patients, which mandated requesting a monitoring test that could give them an idea regarding the patient's individual response to the medication. However, there were inconsistencies regarding the findings in different studies[7]. Our study explored these clinical parameters to check for the correlation of these clinical parameters and anti-Xa activity level which has been reported in the literature as one of the most important clinical parameters for the activity of DOACs. These parameters included GFR or CrCl, BMI, and age.

Primary: In a recent pharmacokinetic study of apixaban, 31% lower peak concentrations were found in patients with a weight above 120 kg, or a BMI above 30 kg/m2 [7]. Another study evaluated renal function for 913 patients including patients at extremes of body weights (>120 kg and < 50 kg), and it was found that renal function was the best predictor for rivaroxaban activity, while body weight didn't have major effects on level[8]. In our study, kidney function, age, and weight did not show a significant correlation with anti-Xa activity.

Secondary: In an observational study that was done recently to evaluate the association of DOACs with different clinical parameters, among 565 patients with atrial fibrillation, thrombotic complications occurred specifically in patients with the lowest trough levels (36-108 ng/mL)[9]. Another study evaluated the quality of anticoagulation in patients who developed acute ischemic stroke, low DOACs levels (<50 ng/mL) were shown to be a predictor of disease severity and large vessel occlusion when compared to high DOAC plasma levels[10]. Thrombosis had a weak positive correlation with anti-Xa level in our study, however, bleeding has shown semi strong positive correlation with anti-Xa activity level. The questionable absorptive capacity of oral anticoagulants due to bowel resection was found to be as the indication for testing among 23.25% of the samples, followed by renal dysfunction in 15.11% of the samples, minor and major bleeding in 13.95% and 11.62% of the cases respectively, while an elevation in the INR was the indication for 8.13%.

There is still no clear pattern or clinical parameters that may necessitate testing for anti-Xa level for patients on DOACs. However, testing for anti-Xa activity when a DOAC is suspected to be causing bleeding could be helpful for clinicians to decide regarding how to manage the patient and whether another factor could be causing the bleeding. Until now, there is no standardized recommendations for adjusting the medications' doses based on the anti-Xa level, and this could be attributed the variability of the levels with different clinical outcomes and when correlated to different clinical parameters.

ABCB1 gene polymorphisms (which encodes p-glycoprotein), was studied in different clinical studies. One of the polymorphisms (rs1045642) has been shown to affect the metabolism of rivaroxaban[11], while ABCB1 rs4148738 was shown to result in significant variability in peak levels of apixaban[12]. A recent case report has concluded that patients who are homozygous to haplotype (C.2677G>T; TT and C.3435C>T; TT) can have an increase in the plasma concentration of rivaroxaban as well as a longer half-life[13]. Variations in sulfotransferases (SULTs) (a pathway that affects the metabolism of apixaban) were shown in another study to affect the estimated active apixaban levels[14]. These different pharmacogenetic variations could affect the metabolism and activity of these medications, which could explain the inconsistency in correlating anti-Xa activity levels with the tested clinical parameters and clinical outcomes[15].

Strengths and limitations: Our study is unique since it tries to fill a real gap in clinical practice where clinicians are questioning the efficacy and safety of these medication while accounting for different variables that could affect their activities. Our study has also investigated the indications of testing which has not been investigated before and which could help guide level monitoring based on the appropriate indications. This study is a single-centered study and included a small number of patients who had DOACs anti-Xa activity levels measured at different points in time without standardization of the timing of testing.

Future directions: One of the important points which makes DOACs an attractive option for clinicians and patients is that it has been always labeled as medications which don't need adjustment. Moreover, many clinicians and patients think of DOACs as safe medications since they weren't linked historically to any test. Therefore, one of the future directions could be to measure patients' willingness to do testing for DOACs. In addition, testing of DOACs needs further large-scale studies to investigate its validity and decide the most appropriate, most efficient, and most cost-effective testing method for the activity of the medications. Standardizing the testing for DOACs could result in multiple centers starting to adopt the testing method recommended by different well-trusted clinical guidelines, and therefore more opportunity to investigate the measuring of the medications' activity or levels. The development of point of care DOACs' activity/level testing can help in reaching more patients and in providing more comprehensive evidence regarding whether DOACs' activity and plasma levels can be dependable to make clinical decision or not.

Conclusion

Clinical parameters such as age, CrCl, BMI, and body weight as well as the incidence of thrombosis didn't show a strong or statistically significant correlation with anti-Xa activity level, while testing in case of bleeding has shown a semi strong correlation. Moreover, it has shown to correlate with some hemostasis assays. More robust studies are needed to evaluate this correlation and help guide clinicians to making clinical decisions.

Table 1. Baseline Characteristics.

Characteristic	Median	IQR	Total (%) N = 80
Sex **Male**			41 (51.25)
Age	62.5	(51 - 75.5)	
Weight (kg)	73.0	(65.5 – 86)	
Height (cm)	164.0	(156 – 172)	
BMI (kg/m2)	26.7	(23.5 – 31.3)	
GFR (mL/min/1.73 m2)	60.0	(38 – 90)	
CrCl (mL/min)	65.9	(32 – 113)	
Past Medical History			
Hypertension			44 (55)
Diabetes Mellitus			39 (48.75)
Atrial Fibrillation			34 (42.5)
Solid Tumor			25 (31.25)
Colon cancer			10 (12.5)
Pancreatic cancer			7 (8.75)
Breast cancer			4 (5)
Gastric cancer			3 (3.75)
Nasopharyngeal cancer			1 (1.25)
Coronary Artery Disease			20 (25)
Heart Failure			19 (23.75)
Chronic Kidney Disease			17 (21.25)
Dyslipidemia			16 (20)
Factor V Leiden			5 (6.25)
Acute Kidney Injury			4 (5)
Antiphospholipid Syndrome			4 (5)
Liver Cirrhosis			3 (3.75)
Sickle Cell Anemia			3 (3.75)
Other			42 (52.5%)
Patient's past surgical/interventions history			
Bowel resection			25 (31.25)
Coronary Artery Bypass Grafting (CABG)			8 (10)
Gastrectomy			5 (6.25)
Implantable Cardioverter Defibrillator (ICD) insertion			4 (5)
Multi-visceral Transplant			3 (3.75)
Percutaneous Coronary Intervention (PCI)			2 (2.5)
Kidney transplant			2 (2.5)
None			31 (38.75)
Patient's current medications which could affect hemostasis and kidney function at the time of testing			
Heparin			13 (16.25)
Aspirin			13 (16.25)
Vancomycin			8 (10)
Tacrolimus			5 (6.25)
Piperacillin/tazobactam			4 (5)
Meropenem			2 (2.5)
Patients on DOACs			
Apixaban			42 (52.5)
Rivaroxaban			38 (47.5)
Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; GFR, glomerular filtration rate *CrCl was calculated by using Cockcroft-Gault formula **GFR was calculated by using the Modification of Diet in Renal Disease (MDRD) equation			

Table 2. Primary outcome spearman correlations anti-factor Xa activity with clinical parameters (N = 80).

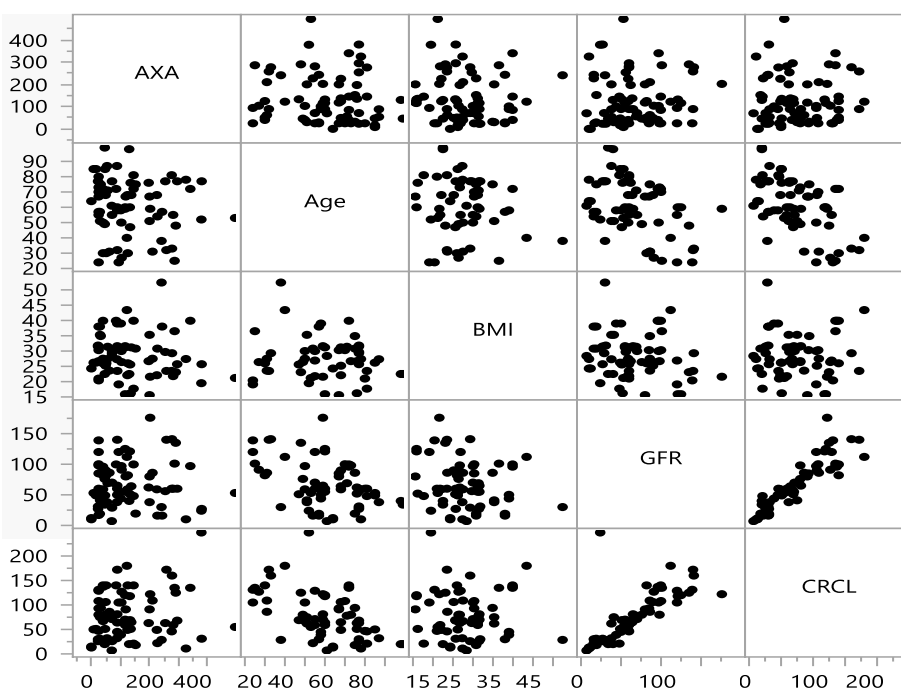| Variable	Spearman Correlation Coefficients	Significance
Age (years)	-0.16120	0.1531
BMI (kg/m2)	-0.09358	0.4090
GFR (mL/min/1.73 m2)	0.14287	0.2061
CrCl (mL/min)	0.18065	0.1088
Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate		

Table 3. Secondary Outcome Correlations anti-factor Xa activity with the development of arterial and venous thromboembolism (within 1 year) and the development of major and minor bleeding (within 3 months) (N = 80).

Variable	Spearman Correlation Coefficients	Significance
Thrombosis	0.05000	0.8296
Bleeding	0.7334	0.4090

Figure 1. Scatterplot for primary outcome spearman correlations anti-factor Xa activity with clinical parameters.

Multivariate Correlations

	AXA	Age	BMI	GFR	CRCL
AXA	1.0000	-0.1269	-0.0486	0.0697	0.1856
Age	-0.1269	1.0000	-0.0761	-0.4378	-0.5499
BMI	-0.0486	-0.0761	1.0000	-0.1602	-0.0261
GFR	0.0697	-0.4378	-0.1602	1.0000	0.7711
CRCL	0.1856	-0.5499	-0.0261	0.7711	1.0000
Abbreviations: AXA, anti-Xa activity; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate. The correlations are estimated by Row-wise method.					

Scatterplot Matrix

Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	
Age	AXA	-0.1612	0.1531	
BMI	AXA	-0.0936	0.4090	
GFR	AXA	0.1429	0.2061	
CRCL	AXA	0.1807	0.1088	
Abbreviations: AXA, anti-Xa activity; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate				

Appendix A. Indications of Teting (N = 80).

Indication	Frequency	Percentage
Questionable absorptive capacity of oral anticoagulants*	20	23.25%
Renal Dysfunction	13	15.11%
Minor Bleeding	12	13.95%
Major Bleeding	10	11.62%
Elevated INR	7	8.13%
Venous Thrombosis		
Deep vein thrombosis	5	5.81%
Obesity	3	3.48%
Drug interaction**	2	2.32%
Arterial Thrombosis		
Stroke	1	1.16%
Underweight Patient	1	1.16%
Elderly***	1	1.16%
Liver cirrhosis	1	1.16%
Undocumented	4	4.65%
Abbreviations: INR, international normalized ratio		

Appendix B. Correlation of the coagulation assays with anti-Xa activity (N = 80).

Variable	Spearman Correlation Coefficients	Significance	Number of samples
INR	0.24951	**0.0276**	78
PTT	0.09325	0.4294	78
PTT Ratio	0.11203	0.3419	78
PT	0.21657	0.0620	78
D-Dimer	0.60000	0.2080	6
Fibrinogen	0.40000	0.6000	4
Abbreviations: INR, international normalized ratio; PT, prothrombin time; PTT, partial prothrombin time			

Appendix C. Action taken if anti-Xa activity level was out of range (N = 80).

Anti-Xa activity	Number of samples	Action taken	Number of samples
High	4 (5%)	Dose changed	2
		Medication Discontinued	0
		No change	2
Normal	65 (81.25%)	Dose changed	9
		Medication Discontinued	1
		No change	55
Low	11 (13.75%)	Dose changed	5
		Medication Discontinued	0
		No change	6

Appendix D. Action taken if anti-Xa activity level was out of range (N = 15).

	Dose	Normal Range (ng/ml)	Number of samples out-of-range	Indications of testing for out-of-range results
Anti-Xa Activity for Apixaban	**2.5 mg**	30 – 153	**0 (high)**	
			5 (low)	**Major bleeding and renal dysfunction (2)** **Minor bleeding (3)**
	5 mg	59 – 302	**4 (high)**	**Minor bleeding (1)** **Major bleeding (1)** **Renal dysfunction (1)** **Undocumented (1)**
			6 (low)	**Venous thrombosis and renal dysfunction (4)** **Major bleeding (1)** **Questionable absorptive capacity of oral anticoagulants (1)**
Anti-Xa Activity for Rivaroxaban	**20 mg**	22 – 535	**0 (high)**	
			0 (low	

Appendix E. Correlations of anti-Xa activity with clinical parameters based on the indication (N = 80).

Indications	N samples	Age	BMI	GFR	CrCl
Major bleeding	**10**	r = -0.08926 p = 0.8063	r = -0.20989 p = 0.5606	r = -0.13720 p = 0.7055	r = 0.06812 p = 0.8517
Minor bleeding	**12**	r = -0.44296 p = 0.1493	r = 0.30007 p = 0.3433	r = 0.26667 p = 0.4021	r = 0.49825 p = 0.0992
Venous thrombosis	**5**	r = -1.00000 p = <.0001	r = 1.00000 p = <.0001	r = 0.72548 p = 0.1654	r = 0.72548 p = 0.1654
Renal dysfunction	**13**	r = 0.15887 p = 0.6042	r = 0.23830 p = 0.4330	r = 0.33662 p = 0.2607	r = 0.16505 p = 0.5900
Obesity	**3**	r = -1.00000 p = <.0001	r = -0.50000 p = 0.6667	r = -0.50000 p = 0.6667	r = -0.50000 p = 0.6667
Elevated INR	**7**	r = -0.28571 p = 0.5345	r = -0.14286 p = 0.7599	r = -0.53571 p = 0.2152	r = -0.07143 p = 0.8790
Questionable absorptive capacity of oral anticoagulants	**20**	r = 0.03071 p = 0.8977	r = -0.37968 p = 0.0987	r = 0.02791 p = 0.9070	r = -0.08035 p = 0.7363
Abbreviations: INR, international normalized ratio					

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