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First Evidence: TRAP-Induced Platelet Aggregation Is Reduced in Patients Receiving Xabans

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Abstract

The availability of direct oral anticoagulants has caused a paradigm shift in the management of thrombosis. Rivaroxaban and apixaban are 2 direct oral anticoagulants whose target specificity is activated factor X (FXa). However, it is still not fully understood if and how xabans impact platelet function. This observational study aimed to assess the in vitro platelet function in patients with atrial fibrillation receiving xabans. This was a single-center study quantifying platelet aggregation in 41 patients treated with apixaban or rivaroxaban by light transmission aggregometry. The thrombin receptor activating peptide (TRAP)-induced platelet aggregation was significantly lower 2 hours after taking rivaroxaban or apixaban compared to baseline value (56.15% [8.53%] vs 29.51% [12.9%]; $P = .000$). Moreover, concomitant use of angiotensin-converting enzyme blockers, proton pump inhibitors, and statins reduces the efficiency of xabans. The TRAP-induced platelet aggregation was reduced in patients with cardiovascular disease 2 hours after receiving xabans.

Keywords

aggregation, xabans, DOACs, platelet

Introduction

Atrial fibrillation (AF) increases the risk of ischemic stroke by 5-fold and is associated with 15% of strokes in all age-groups and 30% in persons older than 80 years.[1] Patients with AF-related stroke have higher recurrent risk, morbidity, and mortality when compared to patients with other stroke types.[2] Current guidelines emphasize stroke prevention in patients with AF, in the presence of stroke risk factors.[3] Effective stroke prevention essentially refers to oral anticoagulation. The use of vitamin K antagonists (VKAs) reduces stroke/systemic embolism by 64% and all-cause mortality by 26%, compared to control or placebo.[4] However, the use of VKAs has many limitations, including the need to ensure proper anticoagulation control by regular monitoring, given VKAs' many interactions with drugs and diet.[5] As a result, 30% to 50% of patients with AF were undertreated.[6] To overcome the limitations of VKAs, the direct oral anticoagulants (DOACs) have been introduced and offer relative efficacy, safety, and convenience compared to VKA therapy.[7] The available DOACs, dabigatran, rivaroxaban, apixaban, and edoxaban, were approved by the US Food and Drug Administration in October 2010, November 2011, December 2013, and January 2015, respectively.

Rivaroxaban and apixaban are 2 DOACs whose target specificity is activated factor X (FXa), which is why they are referred to here as xabans.[8-10] The mechanism of action of rivaroxaban and apixaban is the inhibition of prothrombinase complex-bound and clot-associated FXa, resulting in a reduction of the thrombin burst during the propagation phase of the coagulation cascade. Thrombin is an essential enzyme in the coagulation system and it is also the strongest endogenous platelet agonist.[11] Effect of thrombin on platelets is mainly mediated by 2 G-protein-coupled receptors, protease-activated receptor 1 (PAR1) and PAR4.[12] Mechanistically, thrombin proteolytically cleaves a part of the extracellular loop

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Table 1. Clinical Baseline Characteristics of the Patients.

Characteristics	Number of Patients or Value
Number of patients	
Apixaban	20
Rivaroxaban	21
Age, years, mean (SD); range	74.85 (9.32); 55-94
≤65 years	7
>65 years	34
Sex	
Male	19
Female	22
Indication	
Atrial fibrillation	41
Valvular	0
Nonvalvular	41
Paroxysmal	16
Persistent	14
Permanent	11
Dose	
Apixaban 5 mg twice daily	13
Apixaban 2.5 mg twice daily	7
Rivaroxaban 15 mg once daily	21
Positive medical history:	
Diabetes mellitus	20
Arterial hypertension	41
Renal disease	21
Dialysis, transplant, creatinine >2.26 mg/dL or >200 μmol/L	1
Liver disease	10
Cirrhosis or bilirubin >2× normal with AST/ALT/AP >3× normal	0
Cerebral stroke/transient ischemic attack history	13
Coronary artery disease	11
One vessel	5
Two vessels	6
History of pulmonary embolism	1
Myocardial infarction history	13
Body mass index, kg/m^2	
Normal weight (18.5-24.9)	17
Overweight (25.0-29.9)	8
Obese (30.0-39.9)	16
Ischemic heart disease—Classification according to the New York heart association (NYHA)	
I	0
II	25
III	15
IV	1
CHA_2DS_2VASc score, mean (SD); range	3.83 (1.24); 2-7
2	5
3	13
4	13
5	5
6	4
7	1
HAS-BLED score, mean (SD); range	1.76 (0.89); 1-5
1	18
2	18
3	3
4	1
5	1
Platelets × 10^9/L, range × 10^9/L	240 (158-321)
Creatinine, μmol/L, mean (SD)	113.66 (36.24)
Male	
Normal (55-100)	5
Elevated (>100)	14
Female	
Normal (44-95)	13
Elevated (>95)	9
ALT, μkat/L, mean (SD)	0.39 (0.38)
Normal (0.1-0.6)	35
Elevated (>0.6)	6
AST, μkat/L, mean (SD)	0.42 (0.33)
Normal (0.1-0.6)	37
Elevated (>0.6)	4
Gamma glutamyltransferase (γGT), μkat/L, mean (SD)	1.12 (1.54)
Normal (0.07-0.63)	24
Elevated (>0.63)	17
Drugs	
β-Blockers	28
Calcium channel blockers	11
Angiotensin-converting enzyme blockers	23
Angiotensin II receptor antagonists	10
Antiplatelet drugs	0
Proton pump inhibitor	30
Statins	16

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; SD, standard deviation.

of these receptors. It mediates platelet aggregation, calcium mobilization, and platelet shape change, ultimately resulting in activation of the platelet glycoprotein (GP)IIb/IIIa receptor.[13-15] xabans do not directly affect platelet aggregation induced by collagen or adenosine diphosphate, but by inhibiting FXa, they indirectly decrease clot formation induced by thrombin.[16,17] Therefore, the aim of the present study was to assess the effects of xabans on in vitro platelet aggregation in patients with nonvalvular AF.

Materials and Methods

The local ethical committee of the Jessenius Faculty of Medicine in Martin approved this study (EK 1702/2015). All study participants agreed to participate in the project and signed a written informed consent in accordance with the Declaration of Helsinki.

Rivaroxaban was administered at fixed 15 mg once-daily dose (at 7:00 AM). This study also tested apixaban administered at twice-daily dose of 2.5 or 5 mg (at 7:00 PM and 7:00 AM). Blood samples were taken before drug dose administration (sample 1, at 7:00 AM) for the assessment of the apixaban or rivaroxaban trough level and 2 hours later (sample 2, at 9:00

Table 2. Correlation Between TRAP-Induced Platelet Aggregation and Antifactor Xa (Rivaroxaban) and Antifactor Xa (Apixaban) in Samples 1 and 2.[a]

		Antifactor Xa (Sample 1)	TRAP-Induced Platelet Aggregation (Sample 1)
(A) Correlation between TRAP-induced platelet aggregation and antifactor Xa (rivaroxaban) in sample 1			
TRAP-induced platelet aggregation (sample 1)	Pearson correlation	1	−0.317
	Significance (2 tailed)		0.162
Antifactor IIa (sample 1)	Pearson correlation	−0.317	1
	Significance (2 tailed)	0.162	
(B) Correlation between TRAP-induced platelet aggregation and antifactor Xa (rivaroxaban) in sample 2			
TRAP-induced platelet aggregation (sample 2)	Pearson correlation:	1	−0.312
	Significance (2 tailed)		0.169
Antifactor IIa (sample 2)	Pearson correlation:	−0.312	1
	Significance (2 tailed)	0.169	
(C) Correlation between TRAP-induced platelet aggregation and anti-factor Xa (apixaban) in sample 1			
TRAP-induced platelet aggregation (sample 1)	Pearson correlation	1	0.328
	Significance (2 tailed)		0.158
Antifactor IIa (sample 1)	Pearson correlation	0.328	1
	Significance (2 tailed)	0.158	
(D) Correlation between TRAP-induced platelet aggregation and antifactor Xa (apixaban) in sample 2			
TRAP-induced platelet aggregation (sample 2)	Pearson correlation	1	0.134
	Significance (2 tailed)		0.573
Antifactor IIa (sample 2)	Pearson correlation:	0.134	1
	Significance (2 tailed)	0.573	

Abbreviation: TRAP, thrombin receptor activating peptide.
[a]Correlation is significant at the 0.01 level (2 tailed).

AM) for the assessment of the apixaban or rivaroxaban peak level. To be sure that the drug was administered at the right time, we implemented the following measures. First, the drug was administered to the patients by a physician who was involved in this study. Second, treatment with xabans was monitored by anti-Xa assay for rivaroxaban or apixaban according to the manufacturer's instructions. All patients on xabans therapy included in our study were hospitalized in the First Department of Internal Medicine during July and November 2016. We do not have any selection criteria. The study investigators had no influence on drug choice (rivaroxaban or apixaban) or dosage. Concomitant treatment (eg, β-blockers, proton pump inhibitor, and so on) was administered immediately after taking the morning dose of xabans.

Light transmission aggregometry (LTA) was performed using the international protocol for the laboratory investigation of platelet function.[18] We wanted to emphasize that testing was performed on patients without any antiplatelet or nonsteroidal anti-inflammatory drugs (10-14 days before measurement) and with normal platelet count ($\geq 150 \times 109$/L). The antecubital venous blood was collected into tubes containing 3.2% buffered sodium citrate (anticoagulant–blood ratio 1:9) to assess platelet aggregation. Platelet aggregability was tested with platelet-rich plasma using platelet aggregometry (PACKS-4 aggregometer; Helena Laboratories, Beaumont, USA). Blood samples were stimulated with thrombin receptor activating peptide (TRAP; 10 μmoL).

Data are presented as numbers with frequencies for categorical variables and means with standard deviations (SD) for continuous variables. For comparison of the different groups, the closed test principle was used. An overall comparison was performed, followed by pairwise comparison if the results were significant. All tests were 2-tailed, and P values <.05 were considered statistically significant. Data were analyzed with SPSS 21.0.0.0 (SPSS Inc, Chicago, Illinois).

Results

Table 1 presents full clinical baseline characteristics of the patients. Forty-one patients with nonvalvular AF were enrolled. The mean age was 74.85 (9.32) years (range: 55-94 years), 22 patients were women, and the mean CHA_2DS_2-VASc score was 3.83 (1.24). All patients began treatment with apixaban or rivaroxaban as initial anticoagulant treatment. The minimum term use of xabans was 18 days. Apixaban doses were 5 mg (65%) or 2.5 mg (35%) twice daily. The mean apixaban concentration was 66.48 (34.22) ng/mL in sample 1 and 151.56 (41.54) ng/mL in sample 2. Concentrations of rivaroxaban in serum (sample 1) were 45.92 (36.86) ng/mL and 195.53 (96.18) ng/mL 2 hours after administration (sample 2). The TRAP-induced platelet aggregation did not correlate significantly with apixaban or rivaroxaban levels (see Table 2). Through subgroup analysis, we found that apixaban significantly reduced the TRAP-induced platelet aggregation more than rivaroxaban. Subgroup analysis showed a significant reduction in TRAP-induced platelet aggregation after administration of angiotensin-converting enzyme blockers, proton pump inhibitors, and statins (see Table 3).

Table 3. Subgroup Analysis.

Subgroup Analysis	TRAP-Induced Platelet Aggregation[a]	*P* Value
Rivaroxaban vs apixaban	Sample 1: 58.81% (9.7%) vs 53.35% (6.1%)	$P = .051$
	Sample 2: 33.81% (11.4%) vs 25.0% (13.2%)	$P = .03$
Rivaroxaban vs apixaban 5 mg twice daily	Sample 1: 58.81% (9.7%) vs 55.46% (5.7%)	$P = .07$
	Sample 2: 33.81% (11.4%) vs 23.85% (11.8%)	$P = .02$
Rivaroxaban vs apixaban 2.5 mg twice daily	Sample 1: 58.81% (9.7%) vs 54.42% (5.1%)	$P = .06$
	Sample 2: 33.81% (11.4%) vs 27.14% (16.2%)	$P = .023$
≤65 years vs >65 years	Sample 1: 96.5% (7.3%) vs 88.4% (10.7%)	$P = .80$
	Sample 2: 82.5% (11.3%) vs 78.6% (14.0%)	$P = .64$
Diabetes mellitus vs without diabetes mellitus	Sample 1: 55.8% (8.6%) vs 56.5% (8.7%)	$P = .80$
	Sample 2: 30.5% (11.4%) vs 28.6% (14.4%)	$P = .64$
With a history of renal disease vs without a history of renal disease	Sample 1: 53.3% (6.9%) vs 59.1% (9.2%)	$P = .51$
	Sample 2: 28.3% (12.3%) vs 30.8% (13.7%)	$P = .54$
With a history of liver disease vs without a history of liver disease	Sample 1: 53.3% (6.9%) vs 59.1% (9.2%)	$P = .51$
	Sample 2: 28.3% (12.3%) vs 30.8% (13.7%)	$P = .54$
With coronary artery disease vs without coronary artery disease	Sample 1: 54.6% (7.8%) vs 56.7% (8.9%)	$P = .47$
	Sample 2: 32.3% (16.0%) vs 28.5% (11.7%)	$P = .41$
With myocardial infarction history vs without myocardial infarction history	Sample 1: 56.7% (5.6%) vs 58.2% (8.9%)	$P = .21$
	Sample 2: 26.5% (12.6%) vs 30.9% (13.0%)	$P = .32$
Normal weight vs overweight and obese	Sample 1: 56.1% (7.4%) vs 56.2% (9.4%)	$P = .99$
	Sample 2: 28.4% (13.6%) vs 30.3% (12.7%)	$P = .63$
Overweight vs obese	Sample 1: 57.7% (11.5%) vs 55.3% (8.3%)	$P = .56$
	Sample 2: 28.0% (16.8%) vs 31.7% (9.8%)	$P = .50$
Normal creatinine level vs elevated creatinine level	Sample 1: 57.4% (7.7%) vs 54.5% (8.9%)	$P = .28$
	Sample 2: 28.4% (11.0%) vs 29.5% (14.1%)	$P = .79$
Normal AST level vs elevated AST level	Sample 1: 55.9% (8.8%) vs 58.5% (5.4%)	$P = .57$
	Sample 2: 30.1% (12.6%) vs 24.0% (16.0%)	$P = .38$
Normal ALT level vs elevated ALT level	Sample 1: 55.7% (8.7%) vs 59.0% (7.1%)	$P = .38$
	Sample 2: 29.4% (12.5%) vs 30.3% (16.4%)	$P = .87$
Normal γGT level vs elevated γGT level	Sample 1: 55.8% (8.5%) vs 56.7% (8.7%)	$P = .73$
	Sample 2: 27.6% (13.0%) vs 32.2% (12.7%)	$P = .27$
β-Blockers vs no β-blockers	Sample 1: 55.0% (7.0%) vs 58.7% (11.1%)	$P = .2$
	Sample 2: 29.9% (13.4%) vs 28.8% (12.2%)	$P = .8$
Calcium channel blockers vs no calcium channel blockers	Sample 1: 57.1% (8.4%) vs 55.8% (8.7%)	$P = .67$
	Sample 2: 26.5% (12.3%) vs 30.6 (13.2%)	$P = .37$
Angiotensin-converting enzyme blockers vs no angiotensin-converting enzyme blockers	Sample 1: 54.87% (9.1%) vs 57.8% (7.7%)	$P = .28$
	Sample 2: 25.65% (12.4%) vs 34.4% (12.1%)	$P = .03$
Angiotensin II receptor antagonists vs no angiotensin II receptor antagonists	Sample 1: 55.3% (7.0%) vs 56.4% (9.1%)	$P = .72$
	Sample 2: 36.9% (11.5%) vs 27.1 (12.6%)	$P = .04$
Proton pump inhibitor vs no proton pump inhibitor	Sample 1: 56.0% (8.4%) vs 56.5% (9.2%)	$P = .86$
	Sample 2: 32.2% (12.6%) vs 22.2% (11.3%)	$P = .03$
Statins vs no statins	Sample 1: 57.1% (6.7%) vs 55.5% (9.6%)	$P = .6$
	Sample 2: 34.9% (11.2%) vs 26.1% (13.0%)	$P = .03$

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; γGT, gamma glutamyltransferase; TRAP, thrombin receptor activating peptide.
[a]Values are mean (standard deviation) for continuous variables.

As shown in Figure 1, the TRAP-induced platelet aggregation by LTA was significantly reduced in sample 2 compared to sample 1 (56.15% [8.53%] vs 29.51% [12.9%]; $P = .000$). Aggregation results for each patient are shown in Figure 2.

Discussion

To our knowledge, this is the first prospective comprehensive study to test whether the xabans affect TRAP-induced platelet aggregation. This study aimed to analyze the influence of the DOACs apixaban and rivaroxaban on platelet function. Thrombin is a key protein in the cascade of fibrin clot formation and also a potent inducer of platelet aggregation.[18-21] The FXa inhibitors potently and selectively inhibit thrombin formation.[22] Thrombin is capable of activating platelets, which is mediated primarily by the hydrolysis of a G-protein-coupled receptor on the platelet membrane, referred to as PAR-1 and a second receptor (PAR-4) that expresses a lower sensitivity to thrombin.[23] Probably, low concentration of thrombin (blocked FXa cannot activate thrombin) is unable to cleave and activate PAR-1. However, the effects of xabans on platelet aggregation are still not fully understood.

This single-center study quantifies platelet aggregation in 41 patients treated with xabans by LTA. The TRAP-induced

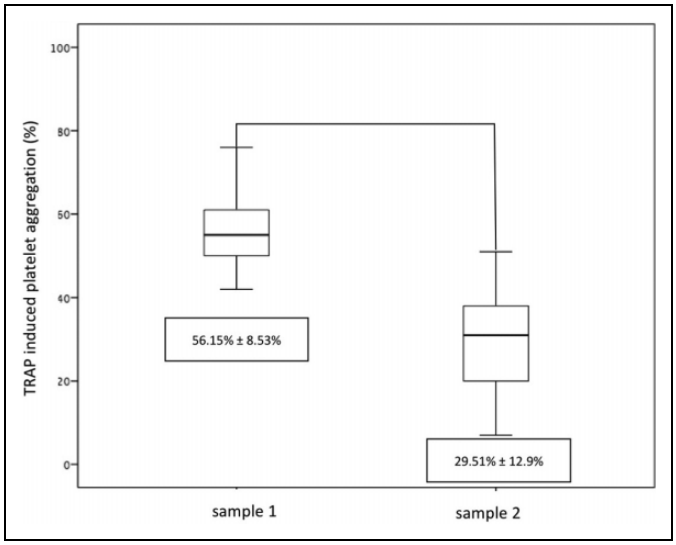

Figure 1. Results of thrombin receptor activating peptide (TRAP)-induced platelet aggregation.

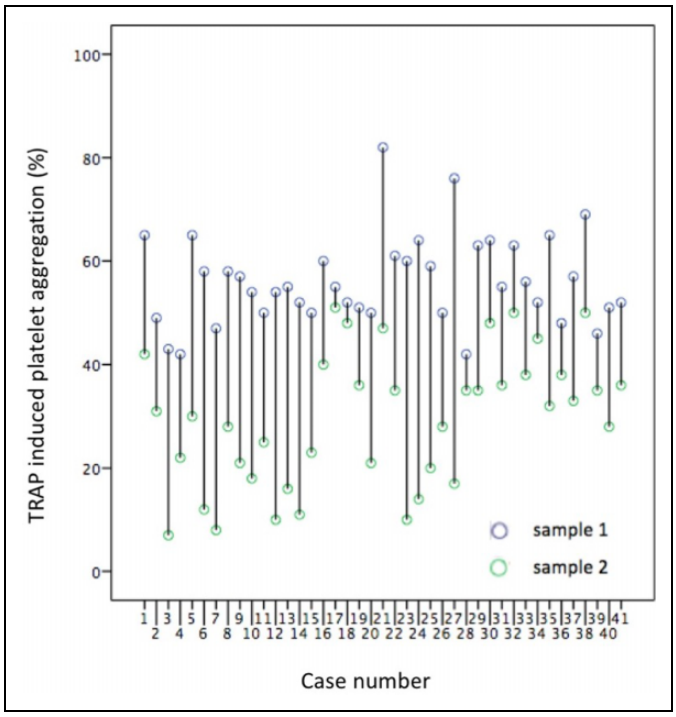

Figure 2. Aggregation results for each patient.

platelet aggregation was significantly lower 2 hours after administration of xabans compared to baseline value (56.15% [8.53%] vs 29.51% [12.9%]). Thus, xabans reduce platelet aggregation by 53% at the time of maximum plasma concentration. However, patients with higher doses of apixaban showed higher TRAP-induced platelet aggregation (Table 3) with dose-dependent characteristics. Nevertheless, no direct association between the apixaban plasma level and TRAP-induced aggregation was found in this study (Table 2). This indicates that the enhanced TRAP-induced platelet aggregation is not necessarily an immediate effect of apixaban but may be explained by the duration of chronic apixaban therapy. In addition, TRAP-induced aggregation should bypass any indirect effect of xabans on thrombin generation. Thus, our data indicate that the TRAP-induced platelet aggregation is enhanced by a chronic, indirect inhibition of thrombin. This might be due to changes in the expression of PAR-1 receptor on the platelets. The same results were observed in study by Olivier et al and Renda et al.[24,25]

No significant differences were found in the patients with a history of renal or liver disease, diabetes, coronary artery disease, myocardial infarction, and so on (see Table 3). It seems that the concomitant use of angiotensin-converting enzyme blockers, proton pump inhibitors, and statins reduces the efficiency of xabans. So far, these interactions have not been seen in any other study.

Our findings could have some important clinical implications because platelet aggregation and coagulation cascade are affected at the same time. The situation could be more worse during concomitant administration of antiplatelet or anticoagulant agents. Moreover, concomitant use of angiotensin-converting enzyme blockers, proton pump inhibitors, and statins reduces the efficiency of xabans. But on the other side, it reduces the impact of xabans on platelet aggregation.

There were several limitations in our study. The small number of participants may have limited the ability to detect small drug effects on platelet function. Second, this study was not powered for clinical outcome. Therefore, it cannot be concluded that, for example, combination of antiplatelet therapy and xabans is not safe. Third, platelet aggregability is greatly affected by preanalytical issues and therefore interpretation of platelet hyperaggregability is potentially accordingly adversely influenced.

Conclusion

In conclusion, our study showed significant effect of xabans on platelet aggregability. Moreover, concomitant use of angiotensin-converting enzyme blockers, proton pump inhibitors, and statins reduces the efficiency of xabans. Future, larger investigations are required to confirm our hypothesis-generating work and correlate them with thrombotic and bleeding clinical events.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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