Apixaban Concentration According to Creatinine Clearance in Non-Valvular Atrial Fibrillation Patients

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Abstract

Background: Apixaban is effective and safe for preventing stroke, and its usage has exponentially increased in recent years. Dose adjustment is based on creatinine level, regardless of creatinine clearance (CrCl). In addition, data concerning therapeutic range of apixaban is limited.

Objectives: The study aimed to determine plasma concentration of apixaban (Cpeak and Ctrough) in patients with both standard-dose and reduced-dose in association with creatinine clearance (CrCl ≥50 ml/min, CrCl <50 ml/min).

Materials and Methods: A prospective observational study was conducted at Phramongkutklao hospital during July 2021 to January 2022. Patients with non-valvular atrial fibrillation (NVAF) who received apixaban were enrolled. Plasma concentrations (Cpeak and Ctrough) of apixaban were tested in individuals who on either standard-dose and reduced-dose. Furthermore, we evaluated apixaban concentration according to CrCl (CrCl ≥50 ml/min and CrCl <50 ml/min).

Results: Total of 34 eligible patients were enrolled. Twenty patients received standard-dose apixaban and 14 patients received reduced-dose apixaban. Median Cpeak and Ctrough in standard-dose group with CrCl ≥50 ml/min were 196 and 129 ng/mL, and levels with CrCl <50 ml/min were 349 and 190 ng/mL. Whereas peak and through levels in reduced-dose group with CrCl ≥50 ml/min were 257 and 104 ng/mL, and with CrCl <50 ml/min were 190 and 108 ng/mL respectively. Therapeutic range of 41-321 ng/ml is recommended as the standard level.

Conclusion: There was no significant difference between trough and peak concentration of apixaban according to creatinine clearance.

Keywords: Direct factor Xa inhibitors, Non-valvular atrial fibrillation, Apixaban concentration, Recurrent ischemic stroke, Bleeding

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Introduction

Direct factor Xa inhibitors oral anticoagulants (DOACs) including rivaroxaban, apixaban and edoxaban have been shown to be equivalent or superior to warfarin for prevention of stroke or systemic embolism and DOACs have lower rates of major bleeding in patients with non-valvular atrial fibrillation (NVAF).[1] DOACs also have less dosing variability, a rapid onset of action and stability.[2,3] Additionally, DOACs do not require routine coagulation monitoring. However, plasma concentration should be measured in patients who suffer some conditions such as trauma, emergency surgery, bleeding or embolic events, and concomitant treatment.[4] Dose monitoring is essentially needed to reduce adverse effects including recurrent infarction because of failure to reach the therapeutic dose or major bleeding caused by over dosage.[3] The standard recommended dose of apixaban is 5 mg taken orally twice daily, but dose reduction will be of 2.5 mg if at least two of the following criteria are met: age ≥80 years, body weight <60 kg, and serum creatinine level ≥1.5 mg/dL.[2-5]

There is insufficient published information regarding the laboratory testing of apixaban. In fact, routine coagulation tests show lower sensitivity to the effect of apixaban including PT and aPTT reagents typically show mild or modest sensitivity.[6] The reliable recommendation for the assessment of apixaban exposure is anti-factor Xa chromogenic assays.[7] A previous study showed a linear correlation between the levels of apixaban concentration and apixaban-specific anti-factor Xa activity (AFXaA).[8] According to EHRA 2018 guidelines, the expected range (P5/95 percentiles) of apixaban in terms of plasma concentration at peak and trough for standard-dose were 69-321 and 34-230 ng/ml.[3]

There are several studies investigating the concentration of apixaban in both doses but data on apixaban concentration specified by serum creatinine clearance is limited. Hence, this study aimed to determine plasma concentration of apixaban (Cpeak and Ctrough) in standard-dose and reduced-dose according to creatinine clearance (CrCl<50 & CrCl≥50).

Objectives

1. To evaluate plasma apixaban concentration (Cpeak and Ctrough) in both standard-dose and reduced-dose apixaban.
2. To evaluate plasma apixaban concentration according to creatinine clearance (CrCl ≥50 ml/min, CrCl <50 ml/min).

Materials and Methods

Study design

This prospective observational study was conducted in inpatient and outpatient departments of Phramongkutklao hospital between August 2021 and January 2022. This project was approved by the Institutional Review Board Royal Thai Army Medical Department no. R046h/64.

Trial Population

We recruited patients with non-valvular atrial fibrillation (NVAF) treated with apixaban. Eligible cases must age above 20 years old and consecutively used unchanged dose of apixaban for at least 7 days. The study excluded patients with severe kidney disease (CrCl<15 ml/min), chronic liver disease (Child-Pugh Class C), thrombocytopenia (platelet<100,000/mm^3),

pregnancy, breastfeeding, prosthetic mechanical heart valve or active bleeding. All patients provided informed consents before enrollment into the study.

Procedures

Total 20 patients taking apixaban 5 mg (standard-dose group) and 14 patients taking apixaban 2.5 mg (reduced-dose group) twice a day were enrolled. Demographics, thromboembolic and hemorrhagic risks according to the scoring system CHA_2DS_2-VASc and HAS-BLED were recorded. Renal function was calculated by using the Cockcrof-Gault equation. Concurrent medications were reviewed and recorded.

Blood sample at peak and trough times were collected in all enrolled cases whenever patients had continued fixed-dose apixaban for more than 7 days. The blood samples for peak concentration (Cpeak) were collected at 3-4 hours after the immediate dose of apixaban and the samples for trough concentration (Ctrough) were collected before the morning dosing. Blood was collected in 3.2% Citrated blood tube and centrifuged. Serums were analyzed by chromogenic assay (BIOPHEN® Heparin liquid reagents ready to use).[10,13] Follow-up visits were regularly scheduled at 3, 4 or 6-month basis in case the patients remained stable without complications. Any bleeding or thromboembolic events were subsequently observed and documented for 12 months.

Outcomes

The primary outcome was differences of plasma concentrations of apixaban in patients who on standard-dose or reduced-dose, and plasma concentrations between patients with CrCl ≥50 ml/min and CrCl <50 ml/min.

Statistical methods

Statistical analysis was evaluated by using SPSS 26.0 statistical software. Descriptive statistics were used in demographic data. Continuous variables were presented as median and ranges. Categorical variables are presented as frequencies and percentages. Comparison of the difference between groups was evaluated by paired t-test or Mann-Whitney U test. Discrete data was described in percentage and analyzed by Chi-square. P-value < 0.05 was considered statistically significant.

Results

From July 2021 to January 2022, a total of 34 eligible patients were enrolled. 20 patients received standard-dose apixaban and 14 patients received reduced-dose apixaban. In standard dose group, 16 patients had CrCl ≥50 ml/min (mean CrCl =66.7 ml/min) and 4 patients had CrCl <50 ml/min (mean CrCl =42.5 ml/min). And in reduced-dose group, 4 patients had CrCl ≥50 ml/min (mean CrCl =54.0 ml/min) and 10 patients had CrCl <50 ml/min (mean CrCl =26.4 ml/min). Patients on reduced-dose apixaban group were older [87 (65-99) vs 71 (57-83) year, p =0.203], had lower body weight [57 (47-67) vs 68 (54-62) kg., p =0.546] and creatinine clearance (CrCl) [54 vs 66 ml/min (CrCl ≥50), p =0.128, 26 vs 42 ml/min (CrCl <50), p =0.565] but no statistically significant difference. However, patients in this group had higher CHA_2DS_2-VASc (p =0.015) and HAS-BLED (p =0.006) scores with statistically significant difference. The baseline characteristics of all patients were shown in Table 1.

The median Cpeak and Ctrough of apixaban in standard-dose group were 213 (148-322) ng/mL and 137 (108-179) ng/mL, respectively. The median Cpeak and Ctrough of reduced-dose apixaban group were 197 (155-289) ng/mL and 108 (83-164) ng/mL, respectively.

Of the 20 patients consuming standard-dose apixaban, 16 patients had CrCl ≥50 ml/min with median Cpeak level of 196 (148-268) ng/mL and Ctrough level of 129 (108-162) ng/mL. 4 patients had CrCl <50 ml/min with median Cpeak level of 349 (175-1,024) ng/mL and Ctrough level of 190 (110-661) ng/mL. There was no significant difference in plasma concentration of apixaban between these two subgroups.

For 14 patients consuming reduced-dose apixaban, 4 patients had CrCl ≥50 ml/min with median Cpeak level of 257 (119-309) ng/mL and Ctrough level of 104 (56-161) ng/mL. 10 patients had CrCl <50 ml/min with median Cpeak level of 190 (155-269) ng/mL and Ctrough level of 108 (87-177) ng/mL. Similarly, there was no significant difference in plasma concentration of apixaban between these two subgroups. Plasma concentration of apixaban (Cpeak and Ctrough) and incidence of recurrent ischemic stroke and bleeding events were shown in Table 2.

Table 1 Baseline characteristics

Characteristics	Standard-dose apixaban 5 mg twice a day (n= 20)	Reduced-dose apixaban 2.5 mg twice a day (n= 14)	*P*-value*
Age - year			
Median (range)	71 (57-83)	87 (65-99)	0.203
Sex - no. (%)			
Male	14 (70)	7 (50)	0.458
Weight - kg			
Median (IQR)	68 (54-82)	57 (47-67)	0.546
CrCl - no. (%)			
≥ 50 ml/min	16 (80)	4 (28.5)	0.249
< 50 ml/min	4 (20)	10 (71.5)	1.000
Mean ClCr - ml/min			
CrCl ≥ 50 ml/min	66.7 (61.8-69.4)	54.0 (53.2-54.9)	0.128
CrCl < 50 ml/min	42.5 (39.7-44.3)	26.4 (21.3-28.9)	0.565
Comorbidity - no. (%)			
Prior stroke	9 (45)	6 (42.8)	1.000
Hypertension	19 (95)	14 (100)	1.000
Dyslipidemia	20 (100)	13 (92.8)	0.412
Post stroke seizure	3 (15)	1 (7.1)	0.283
Vascular dementia	1 (5)	0 (0)	1.000
Alzheimer's disease	0 (0)	1 (7.1)	1.000
CHA_2DS_2-VASc - no. (%)			
1	1 (5)	0 (0)	
2	6 (30)	1 (7.1)	
3	3 (15)	2 (14.3)	
4	1 (5)	3 (21.4)	
5	4 (20)	3 (21.4)	
6	5 (25)	3 (21.4)	
7	0 (0)	2 (14.3)	
Median (range)	4 (3-5)	5 (4-6)	**0.015**

Table 1 Baseline characteristics (cont.)

Characteristics	Standard-dose apixaban 5 mg twice a day (n= 20)	Reduced-dose apixaban 2.5 mg twice a day (n= 14)	*P*-value*
HAS-BLED - no. (%)			
0	2 (10)	0 (0)	
1	7 (35)	3 (21.4)	
2	7 (35)	5 (35.7)	
3	4 (20)	4 (28.6)	
4	0 (0)	2 (14.3)	
Median (range)	2 (1-2)	2 (2-3)	0.006
Indication - no. (%)			
Primary stroke prevention	11 (55)	8 (57.1)	
Secondary stroke prevention	9 (45)	6 (42.9)	
Drug interaction - no. (%)			
Amiodarone	2 (10)	3 (21.4)	
Dronedarone	1 (5)	2 (14.3)	
Ranolazine	1 (5)	1 (7.1)	
Levetiracetam	0 (0)	2 (14.3)	
Vortioxetine	1 (5)	0 (0)	
Paroxetine	0 (0)	1 (7.1)	
Nicergoline	0 (0)	1 (7.1)	

Table 2 Plasma concentration of apixaban (Cpeak and Ctrough) and incidence of recurrent ischemic stroke and bleeding events

Outcomes	Standard-dose apixaban (n=20)			Reduced-dose apixaban (n=14)		
	CrCl ≥ 50 (16)	CrCl < 50 (4)	*p*-value*	CrCl ≥ 50 (4)	CrCl < 50 (10)	*p*-value*
	Plasma apixaban concentration					
Cpeak (ng/mL)	196 (148-268)	349 (175-1,024)	0.682	257 (119-309)	190 (155-269)	0.304
Ctrough (ng/mL)	129 (108-162)	190 (110-661)	0.437	104 (56-161)	108 (87-177)	0.240
	Stroke events					
Ischemic stroke (%)		N/A			1	
Odd ratio (95% CI)			2.92 (0.89-8.15)			
p-value*			0.10			
Hemorrhagic stroke (%)		N/A			N/A	
Odd ratio (95% CI)			N/A			
p-value*			N/A			
	Bleeding events					
Major bleeding (%)		1			N/A	
Odd ratio (95% CI)			1.35 (0.57-3.19)			
p-value*			0.63			
Minor bleeding (%)		N/A			2	
Odd ratio (95% CI)			2.67 (1.71-4.17)			
p-value*			0.081			

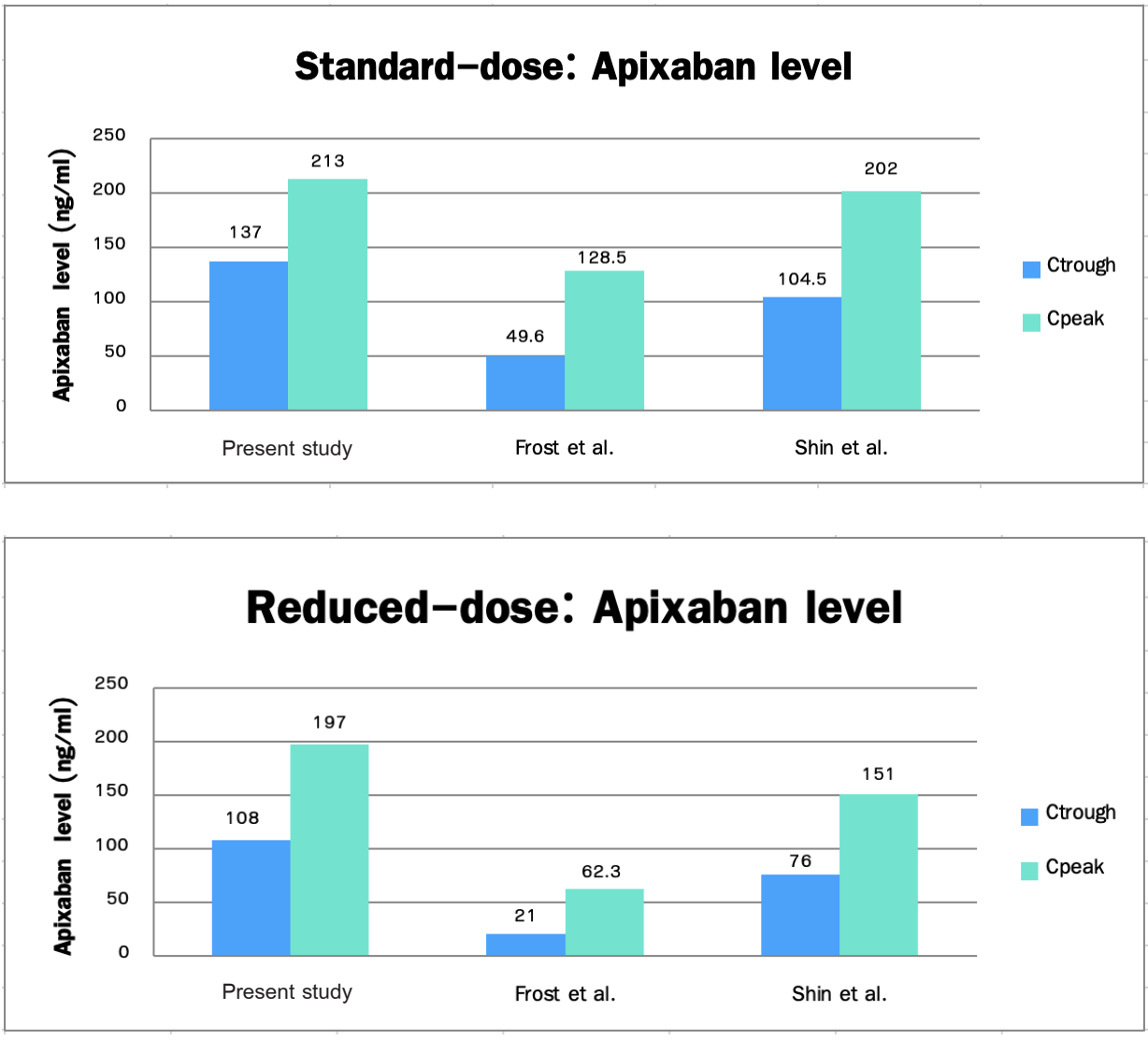
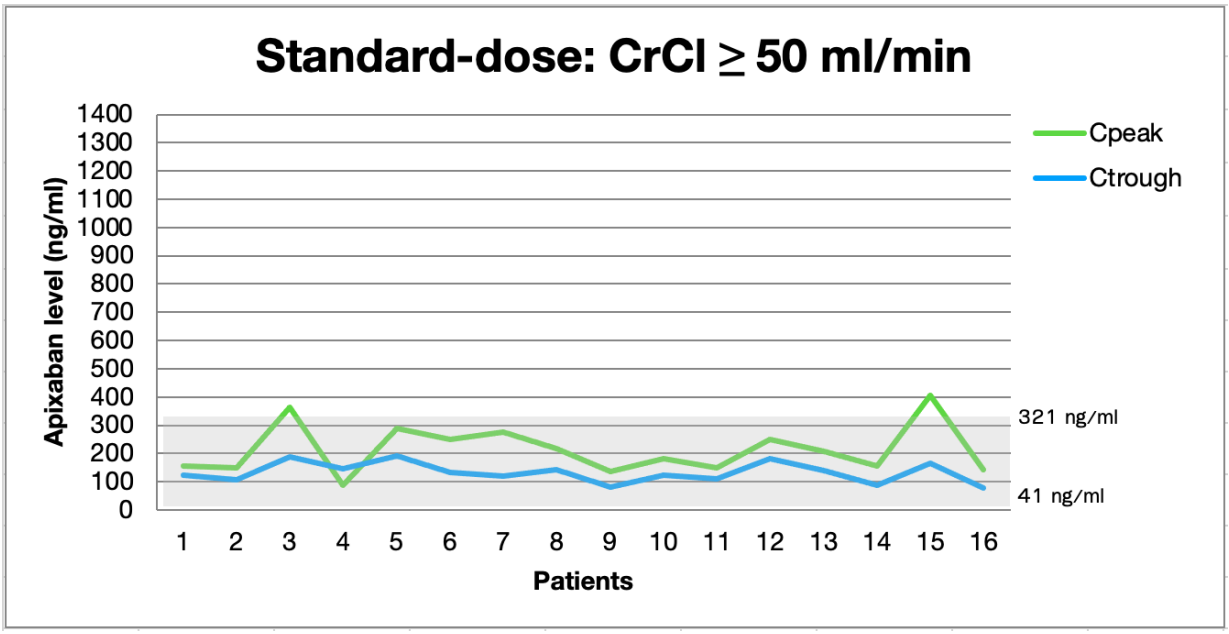
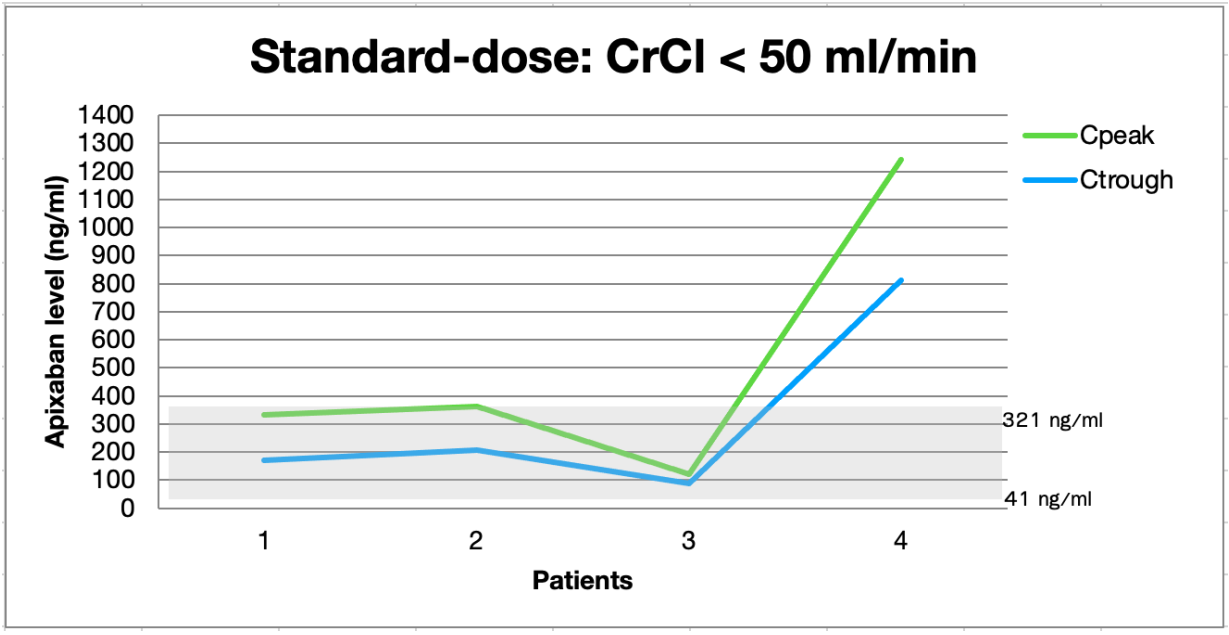
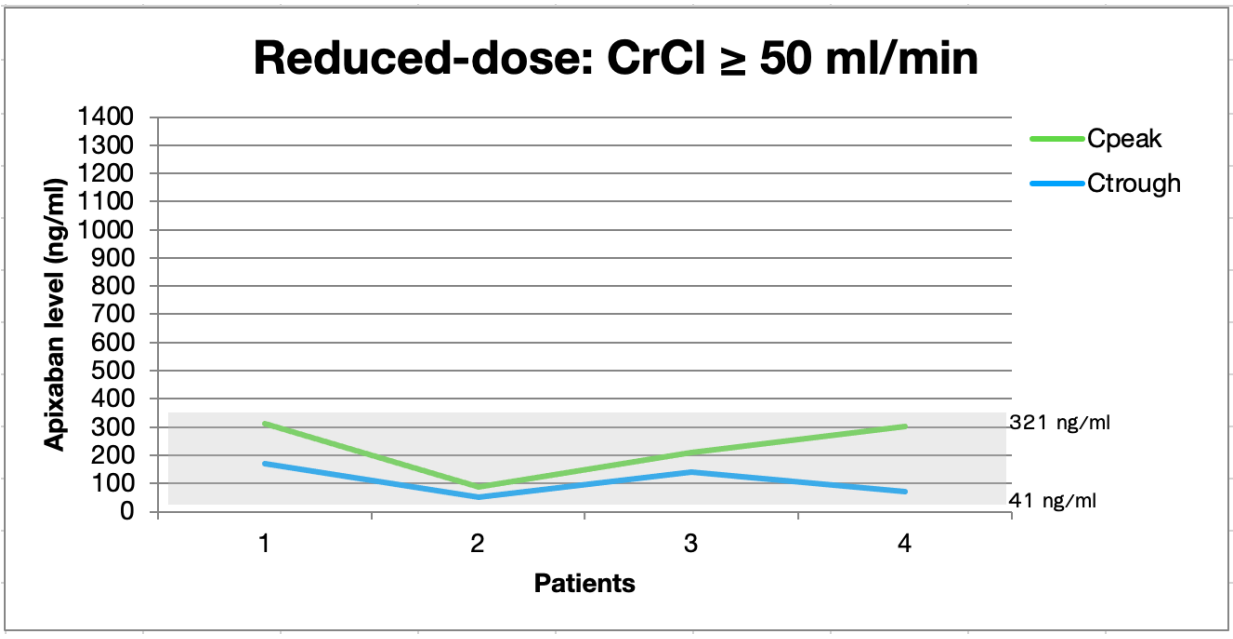


Figure 1 Comparison of the median Cpeak and Ctrough between present study and other studies


Standard-dose: CrCl ≥ 50 ml/min
Apixaban level (ng/ml)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Patients
Cpeak
Ctrough
321 ng/ml
41 ng/ml


Standard-dose: CrCl < 50 ml/min
Apixaban level (ng/ml)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1 2 3 4
Patients
Cpeak
Ctrough
321 ng/ml
41 ng/ml



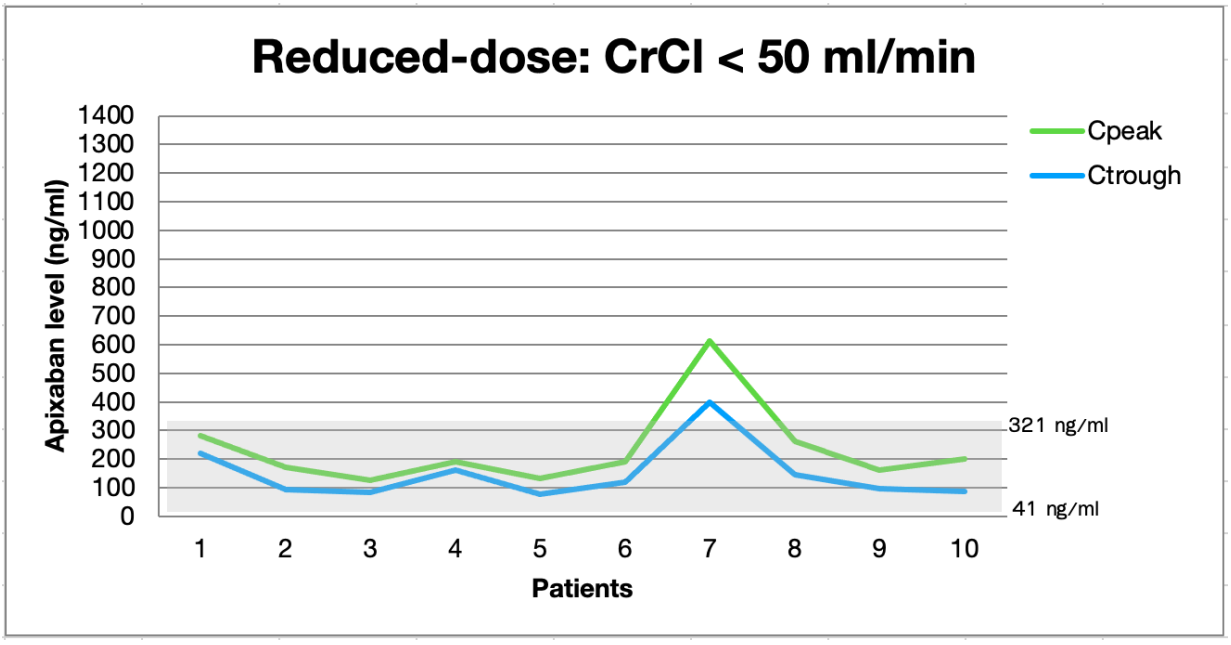


Figure 2 Cpeak and Ctrough level in standard-dose and reduced dose groups with CrCl ≥ 50 ml/min and CrCl <50 ml/min

Discussion

To our knowledge, this is the first study determined the median Cpeak and Ctrough level in NVAF patients treated with apixaban in Thailand. The median Cpeak and Ctrough level of apixaban concentration were 213 (148-322) ng/mL and 137 (108-179) ng/mL respectively in standard-dose group and 197 (155-289) ng/mL and 108 (83-164) ng/mL respectively in reduced-dose group.

Compared with previous studies, the median Cpeak and Ctrough level of apixaban were higher than the level of apixaban concentration in the study in Europe (Frost et al.) (median Cpeak and Ctrough were 128.5 ng/mL and 49.6 ng/mL (p =0.098) at 5.0 mg dose and 62.3 ng/mL and 21.0 ng/mL (p =0.009) at 2.5 mg dose).[9] Our results were comparable to the study from Korea (Hyoshim Shin et al.).[6] Differences of the results can be probably affected by ethnic, geographical or environmental elements that were formerly mentioned in this study. In comparison with the study from Korea (Hyoshim Shin et al.) (median Cpeak and Ctrough were 202.0 ng/mL and 104.5 ng/mL (p =0.671) at the 5.0 mg dose and 151.0 ng/mL and 76.0 ng/mL (p =0.331) at the 2.5 mg dose)[6], our results showed higher plasma concentration in both groups that theoretically caused by lower CrCl.

In standard-dose group and CrCl<50 ml/min, median Cpeak were higher than those standard-dose group with higher CrCl ≥50 ml/min [349 (175-1,024) ng/mL vs 196 (148-268) ng/mL (p=0.437)], however the analysis showed no significant difference. But 2 out of 4 patients with CrCl <50 ml/min in our standard-dose group had Cpeak of apixaban level at upper border of expected range and 1 case had extremely high Cpeak level. In the study on the efficacy and safety of off-label dose according to plasma concentration (Michihiro Suwa et al.), it was found that higher peak plasma apixaban concentration may lead to a greater risk of bleeding and should be an indication for dose reduction.[11] Therefore, patients who use standard-dose of apixaban with CrCl <50 ml/min, especially concomitant use other medication that could increase DOAC level such as amiodarone, SSRI, etc. should be closely monitored of bleeding complications.[12] Therefore, Cpeak measurement may be valuably used to improve the risk-benefit ratio in this group.

In reduced-dose of apixaban group, median Ctrough levels were relatively similar in CrCl ≥50 ml/min and CrCl <50 ml/min groups [104 (56-161) ng/mL vs 108 (87-177) ng/mL (p =0.240)] and median Cpeak level in CrCl ≥50 ml/min were slightly higher than in CrCl <50 ml/min group [257 (119-309) ng/mL vs 190 (155-269) ng/mL (p =0.304)] without significant difference. We noticed that one patient had unexpectedly under dosing with CrCl ≥50 ml/min and had plasma concentration level at lower border of the expected range [Ctrough 51 ng/mL and Cpeak 89 ng/mL, (41-321 ng/mL)]. Therefore, adjusting dose with off-label use should be cautiously monitored.[11] Under dose may potentially lead to failure in preventing thromboembolic events.[13]

From this study, we found that plasma concentration of apixaban in the group of standard-dose with CrCl ≥50 ml/min and reduced-dose with CrCl <50 ml/min group had mostly same levels. That suggests strong influence of CrCl to plasma level of apixaban. In supporting clinical practice, adjusting dose of apixaban according to CrCl would be concerned.

This study has several limitations. It was conducted at a single center with a small number of enrolled patients. Because of COVID-19 pandemic, recruitment was not achieved in time. So the number of cases with side effects were insufficient for statistic analysis on the relationship between apixaban concentration and thromboembolic or bleeding events.

Conclusion

There was no significant difference between trough and peak concentration of apixaban according to creatinine clearance.

Acknowledgements

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