Apixaban Concentration according to Creatinine cle for Stroke prevention in patients with nonvalvular Atrial Fibrillation (ACCESS-AF study)

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ABSTRACT

Background: Apixaban is effective and safe for preventing stroke in the patients with nonvalvular atrial fibrillation (NVAF), and its usage has increased exponentially 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 (peak and trough) in patients with both standard-dose and reduced-dose in association with creatinine clearance (CrCl ≥50 ml/min and CrCl <50 ml/min).

Materials and Methods: A prospective observational study was conducted at Phramong kutklao hospital between July 2021 to January 2024. Patients with nonvalvular atrial fibrillation (NVAF) who received apixaban were enrolled. Plasma concentration (peak and trough) of apixaban were tested in individuals who on either standard-dose or reduced-dose. Furthermore, we evaluated apixaban concentration according to CrCl (CrCl ≥50 ml/min and CrCl <50 ml/min).

Results: Total of 56 eligible patients were enrolled. Thirty-two patients received standard-dose apixaban and 24 patients received reduced-dose apixaban with 75% fulfilled reduced-dose criteria. The median peak and trough levels in patients with CrCl <50 mL/min were 210.23 and 165.70 ng/mL standard-dose group and levels in reduced-dose were 191.01 and 134.19 ng/mL respectively. In patients with CrCl ≥50 mL/min, the levels in standard-dose group were 211.74 and 140.50 ng/mL and in reduced-dose group were 89.11 and 82.27 ng/mL respectively.

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Conclusion: There was significant difference between peak and trough concentration of reduced-dose apixaban in patients with CrCl ≥50 mL/min. To reduce apixaban dose, not only fulfilled the manufacture recommendation, but also concerning of creatinine clearance is important.

Keywords: Apixaban concentration, Creatinine clearance, Reduced-dose apixaban, Standard-dose apixaban

Introduction

Apixaban, one of direct oral anticoagulants (DOAC) initially approved in 2012, has been shown to be equivalent or superior to vitamin K antagonist (VKA) for stroke prevention and has lower rates of major bleeding in patient with nonvalvular atrial fibrillation (NVAF).[1,2] However, adjusted 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 overestimated overdosage.[3,4] In real-world situations, several observational studies considering the effectiveness and safety of reduced-dose apixaban in clinical practice have been reported and found 16-62% of patients received reduced-dose apixaban had higher thromboembolic and hemorrhagic risk score. [5,6]

Currently 3 DOACs including dabigatran,[7] rivaroxaban,[8] and edoxaban[9] are recommended to reduce dose by using creatinine clearance (CrCl). Only apixaban is recommend to reduced dose if at least two of the following three criteria are met including age ≥80 years, body weight ≤60 kg, and serum creatinine (Cr) level ≥1.5 mg/dL (≥133 mmol/L)[2,4,10-12] European guideline suggests reducing apixaban dose by single criteria as creatinine clearance (CrCl) 15-29 mL/min.[2] In fact the renal clearance of apixaban accounts for about 27% of total clearance.[10,13] So, it is important to understand the potential impact of CrCl on apixaban pharmacokinetics and pharmacodynamics to provide appropriately adjusted dose in each patient.

There are several studies investigating the concentration of apixaban in both doses but data on apixaban concentration specified by serum CrCl is limited. Hence, this study aimed to evaluate plasma concentration of apixaban [peak and trough concentration (C_{peak} and C_{trough})] in standard-dose (5mg orally twice daily) and reduced-dose (2.5mg orally twice daily) apixaban according to creatinine clearance (CrCl <50 and CrCl ≥50 mL/min). We also explore whether serum creatinine (<1.5 and ≥1.5 mg/dL), age (<80 and ≥80 years), body weight (≤60 and >60 kg), and sex (female and male) were related to apixaban concentration.

Materials and Methods

Study design

This prospective observational study was conducted in inpatient and outpatient departments of Phramongkutklao hospital between July 2021 and January 2024. This project was approved by the Institutional Review Board Royal Thai Army Medical Department no. R046h/64.

Study population

Participants were recruited from outpatient and inpatient Neurological Department of Phramongkutklao (PMK) Hospital. We enrolled patients with nonvalvular atrial fibrillation (NVAF) treated with apixaban. All patients provided informed consent before enrollment into the study.

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 (including CrCl <15 mL/min), hemodialysis, pre- or post-kidney transplantation, and other specific severe kidney disease), chronic liver disease (Child-Pugh Class C), thrombocytopenia (plasma <100,000/mm^3), other active bleeding conditions, pregnancy or breastfeeding, and prosthetic mechanical heart valve.

Data collection

Total 32 patients taking apixaban 5 mg orally twice daily (standard-dose group) and 24 patients taking apixaban 2.5 mg orally twice daily (reduced-dose group) were enrolled. Demographics, throm boembolic and hemorrhage risks according to the scoring system CHA_2DS_2-VASc and HAS-BLED were recorded. Renal function was calculated by using the Cockcrof-Gault formula abbreviated as creatinine clearance (CrCl). Body weight, serum creatinine (SCr), age, and sex were recorded.

The reliable recommendation for the assessment of apixaban exposure is anti-factor Xa chromogenic assays.[14] A previous study showed a linear correlation between the levels of apixaban concentration and apixaban-specific anti-factor Xa activity (AFXaA).[14] 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 were collected at 3-4 hours after the immediate dose of apixaban and the samples for trough concentration 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 regents ready to use).[15,16] Follow-up visits were regularly scheduled at 3, 4, and 6-month basis in case the patients remained stable without complications. Any bleeding or thromboembolic events were subsequently observed and documented at 3 months.

Statistical analysis

Descriptive statistics were used in the demographic data. Continuous variables were presented as mean, standard deviation (SD), median, and interquartile range (IQR) as appropriate. Categorical variables are presented as frequencies and percentages. The comparison of the difference in continuous variables between groups was evaluated by using an unpaired t-test or the Mann-Whitney U test. Discrete data was described in percentages and analyzed by the Chi-square test. A p value <0.05 (two-sided) was considered statistically significant. All statistical tests were performed using Stata IC15 (StataCorp, 2017, College Station, TX, USA).

Results

Patients

From July 2021 to January 2024, a total of 56 eligible patients were included to the study. Thirty-two patients received standard-dose apixaban and 24 patients received reduced-dose apixaban.

In standard-dose group, 20 patients (62.5%) had CrCl ≥50 mL/min (median CrCl = 63.51 mL/min) and 12 patients (37.5%) had CrCl <50 mL/min (median CrCl = 38.95 mL/min). While in reduced-dose group, 8 patients (33.33%) had CrCl ≥50 mL/min (median CrCl = 72.69 mL/min) and 16 patients (66.67%) had CrCl <50 mL/min (median CrCl = 36.92 mL/min). Patients in reduced-dose apixaban

group were older than standard-dose apixaban group (81.96±9.21 vs 74.06±9.24 years, p value = 0.001), had lower body weight (56.08±12.15 vs 67.03±12.90 kg, p value = 0.002) and had lower CrCl (43.43 vs 55.83 mL/min, p value =0.059). The score of CHA_2DS_2-VASc and HAS-BLED in both reduced-dose and standard-dose apixaban groups were not different. The other baseline characteristics of all patients were shown in Table 1.

Table 1 Baseline characteristic

Characteristics	Total (N = 56)	Reduced-dose apixaban (n = 24)	Standard-dose apixaban (n = 32)	*p*-value
Age – year				
Mean (SD)	77.45 (9.45)	81.96 (9.21)	74.06 (8.24)	0.001
Sex – no. (%)				
Male	30 (53.57)	11 (45.83)	19 (59.38)	0.31
Body weight – kg				
Mean (SD)	62.34 (13.62)	56.08 (12.15)	67.03 (12.90)	0.002
Body mass index – kg/m^2				
Mean (SD)	23.96 (3.98)	22.54 (3.36)	25.02 (4.11)	0.019
Serum creatinine – (mg/dL)				
Mean (SD)	1.14 (0.46)	1.19 (0.60)	1.10 (0.34)	0.490
CrCl – no. (%)				
CrCl <50 mL/min	28 (50.00)	16 (66.67)	12 (37.50)	0.031
CrCl ≥50 mL/min	28 (50.00)	8 (33.33)	20 (62.50)	
Median CrCl – mL/min (IQR)				
All CrCl	51.78 (38.04 – 65.05)	43.43 (30.11 – 59.78)	55.83 (39.97 – 70.10)	0.059
<50 mL/min	38.04 (27.59-43.05)	36.92 (23.05-43.43)	38.95 (35.09-41.61)	0.460
≥50 mL/min	65.06 (57.56-85.02)	72.69 (59.78-86.19)	63.51 (56.14-85.02)	0.480
Comorbidity – no. (%)				
Previous stroke	29 (51.79)	13 (54.17)	16 (50.00)	0.760
Hypertension	52 (92.86)	23 (95.83)	29 (90.62)	0.450
Dyslipidemia	48 (85.71)	18 (75.00)	30 (93.75)	0.047
Diabetes mellitus, type 2	17 (30.36)	6 (25.00)	11 (34.38)	0.450
Congestive heart failure	47 (83.93)	18 (75.00)	29 (90.62)	0.120
Cardiovascular disease	36 (64.29)	17 (70.83)	19 (59.38)	0.380

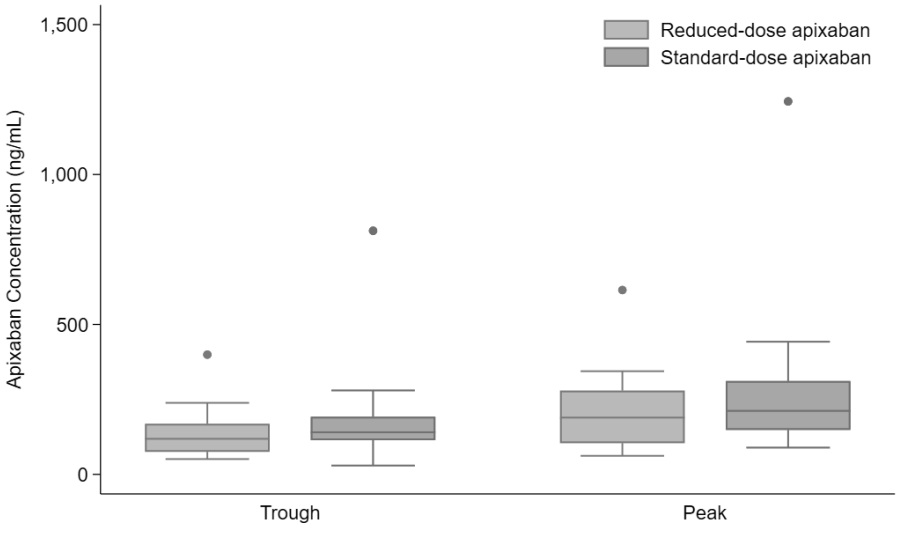
Characteristics	Total (N = 56)	Reduced-dose apixaban (n = 24)	Standard-dose apixaban (n = 32)	*p*-value
CHA_2DS_2-VASc – no. (%)				
0	3 (5.35)	0 (0)	3 (9.38)	
1	1 (1.79)	0 (0)	1 (3.13)	
2	1 (1.79)	0 (0)	1 (3.13)	
3	7 (12.50)	4 (16.67)	3 (9.38)	
4	13 (19.64)	5 (20.83)	8 (25.00)	
5	9 (16.07)	5 (20.83)	4 (12.50)	
6	11 (14.29)	5 (20.83)	6 (18.75)	
7	6 (10.71)	4 (16.67)	2 (6.25)	
8	3 (3.57)	1 (4.17)	2 (6.25)	
Median (IQR)	5 (4-7)	5 (4-7)	5 (3-8)	0.535
HAS-BLED – no. (%)				
1	5 (8.92)	2 (8.33)	3 (9.38)	
2	18 (30.36)	6 (10.71)	12 (37.5)	
3	17 (23.21)	8 (33.33)	9 (23.13)	
4	13 (17.86)	7 (29.17)	6 (18.75)	
5	2 (3.57)	0 (0)	2 (6.25)	
6	1 (1.79)	1 (4.17)	0 (0)	
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-5)	0.535
Stroke prevention – no. (%)				
Primary prevention	29 (51.79)	13 (54.17)	16 (50.00)	0.76
Secondary prevention	27 (48.21)	11 (45.83)	16 (50.00)	

Study outcomes

The median peak and trough concentration of apixaban in standard-dose group were 211.74 (148.28-311.30) ng/mL and 140.50 (113.90-192.17) ng/mL, respectively. The median peak and trough concentration of apixaban in reduced-dose group were 189.31(104.21-279.20) ng/mL and 118.54 (75.18-169.64) ng/mL, respectively. There was no statistically significant difference in peak and trough concentrations of apixaban between the reduced-dose and standard-dose groups. The data was shown in Table 2 and Figure 1.

Table 2 The median (IQR) plasma concentration of apixaban

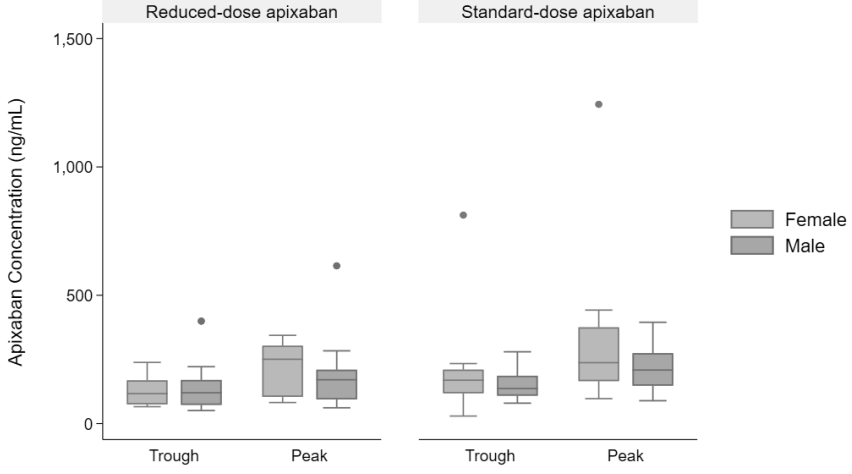
Outcomes	Reduced-dose apixaban (n = 24)	Standard-dose apixaban (n = 32)	*p*-value
Trough (ng/mL)	118.54 (75.18 – 168.64)	140.50 (113.90 – 192.17)	0.085
Peak (ng/mL)	189.21 (104.21 – 279.20)	211.74 (148.28 – 311.30)	0.190



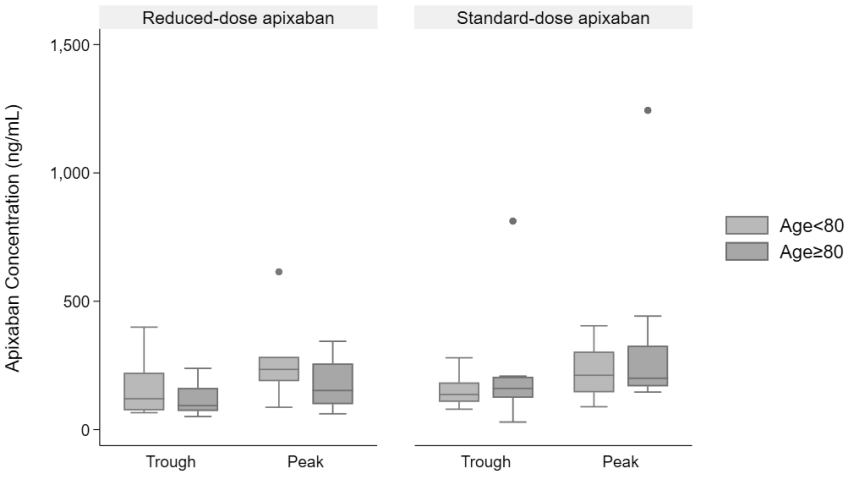
Apixaban concentrations after dosing in patients receiving 2.5mg twice daily (blue) and 5 mg twice daily (pink) are shown on this picture. The trough concentration (reflect the minimum level of anticoagulants, and some minimal thresholds would be expected to be related to efficacy) are on the left and peak concentration (reflect the maximal level of anticoagulant and would be expected to be related to bleeding risk) are shown on the right. The vertical lines indicate median.

Figure 1 Box plot of apixaban concentrations for reduced-dose (2.5 mg) and standard-dose (5 mg) orally twice daily

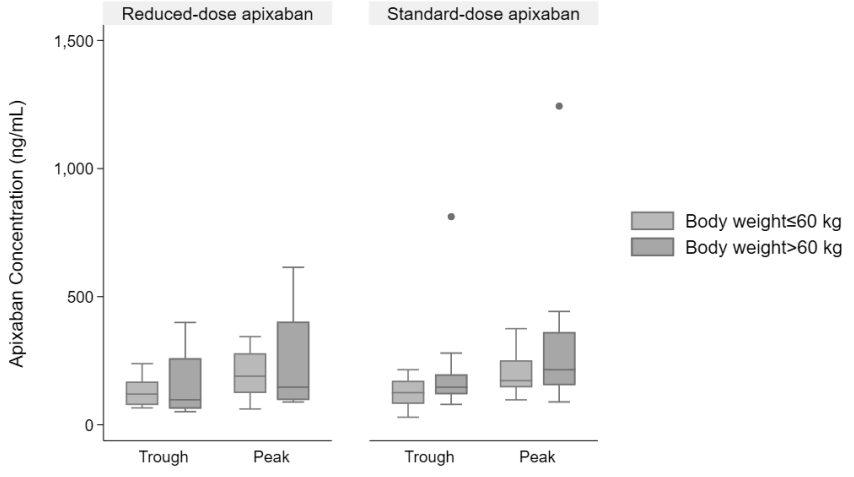
A) Sex (female and male)



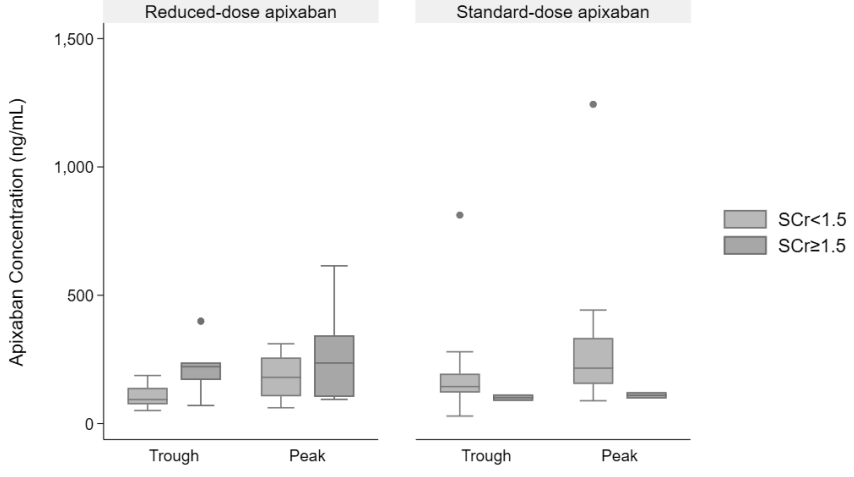
B) Age (age <80 years and age ≥80 years)



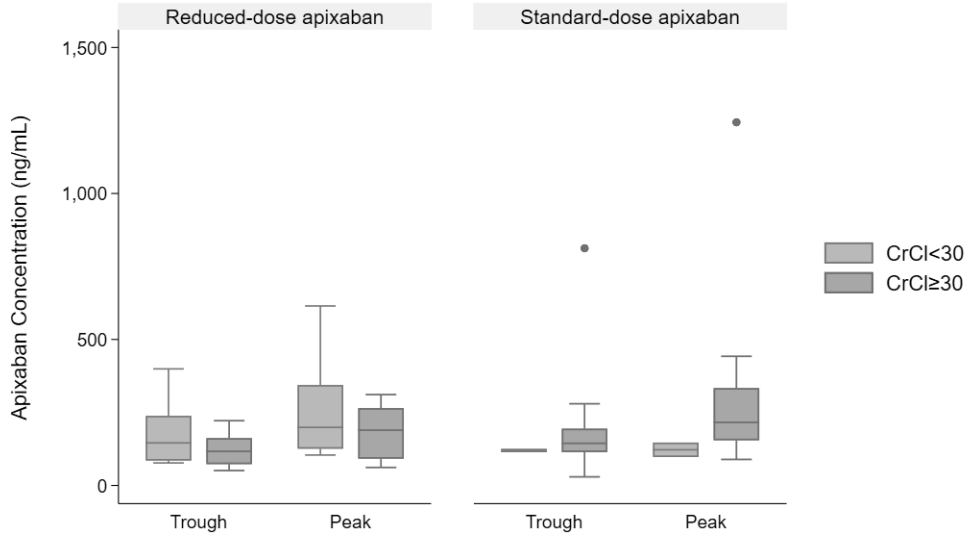
C) Body weight (body weight ≤60 kg and body weight >60 kg)



D) Serum creatinine (SCr <1.5 and SCr ≥1.5)



E) Creatinine clearance (CrCl <30* and CrCl ≥30)



* There is very low data. We have only 2 participants who receive standard-dose apixaban (5 mg oral twice daily), whereas their creatinine clearance is between 15 – 29 mL/min (CrCl <30 mL/min).

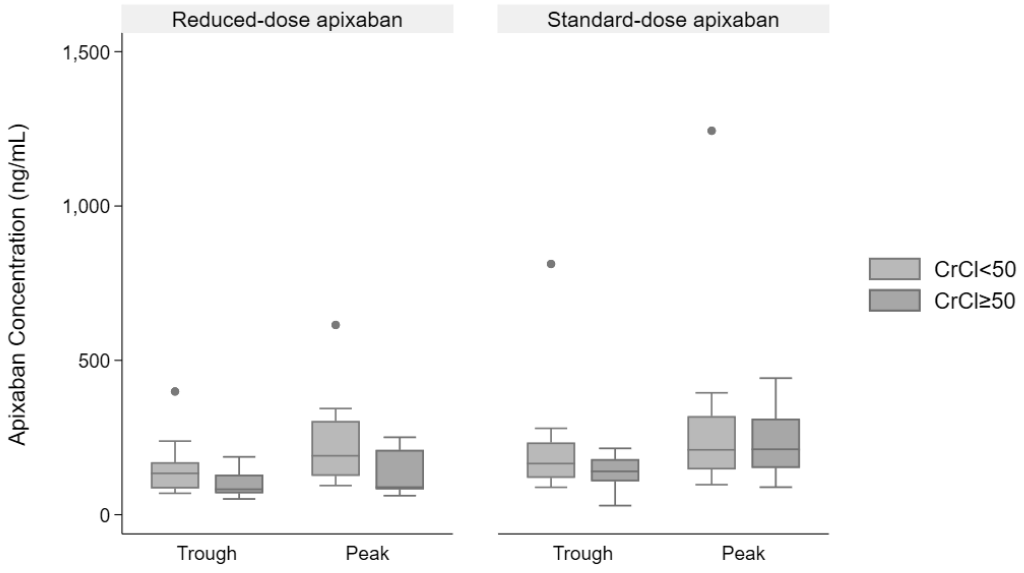
Supplemental Figure 1 Peak and trough apixaban concentrations according to specific conditions (sex, age, body weight, SCr, and CrCl <30 and ≥30 mL/min)

Compare the level of apixaban concentration (peak and trough concentration) between reduced-dose and standard-dose apixaban were shown in Table 3. Of the 32 patients consuming standard-dose vs 24 patients consuming reduced-dose apixaban in the level of CrCl <50 mL/min, the peak level of apixaban concentration in 12 patients consuming standard-dose had median peak level of 210.23 (146.57-319.33) ng/mL vs 15 patients consuming reduced-dose had median peak level of 191.01 (125.84-306.57) ng/mL (p value = 0.92), and the trough level of apixaban concentration in 10 patients consuming standard-dose had median trough level of 165.70 (119.40-233.94) ng/dL vs 14 patients consuming reduced-dose had median trough level of 134.19 (85.18-170.18) ng/dL (p value = 0.27). There was no significant difference in plasma concentration of apixaban level between these two groups.

Table 3 Subgroup analysis of plasma concentration of apixaban in reduced-dose and standard-dose apixaban according to sex, age, body weight, serum creatinine (SCr), and creatinine clearance (CrCl)

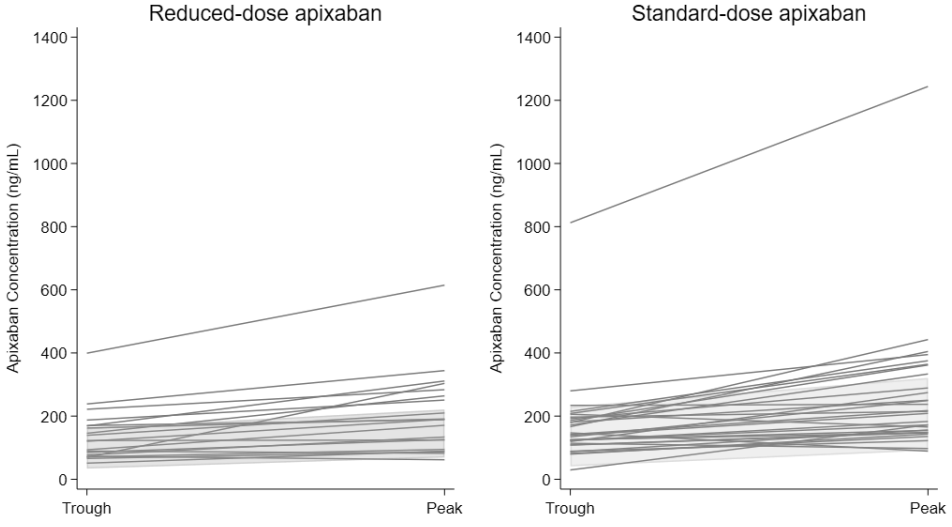
Charac-teristics	Trough concentration (ng/mL)			Peak concentration (ng/mL)		
	Reduced-dose apixaban	Standard-dose apixaban	p-value	Reduced-dose apixaban	Standard-dose apixaban	p-value
Creatinine clearance (mL/min) – median (IQR)						
<50	134.19 (85.18-170-18	165.70 (119.40-235.94)	0.270	191.01 (125.84-303.57)	210.23 (146.57-319.33)	0.920
≥50	82.27 (69.52-129.72)	140.50 (108.48-181.17)	0.047	89.11 (82.16-210.02)	211.74 (151.71-311.30)	0.041
Creatinine clearance (mL/min) – median (IQR)						
<30	145.66 (85.18-238.50)	119.70* (113.90-125.50)	0.700	198.94 (125.84-344.02)	122.17* (97.39-146.95)	0.320
≥30	116.88 (73.06-162.05)	144.43 (114.12-194.49)	0.029	189.31 (91.84-264.99)	216.18 (154.73-333.49)	0.110
Serum creatinine (mg/dL) – median (IQR)						
<1.5	93.38 (75.18-139.23)	144.43 (120.92-194.49)	0.004	180.37 (106.60-257.44)	216.18 (154.73-333.49)	0.056
≥1.5	221.64 (170.18-238.50)	101.35 (88.80-113.90)	0.250	236.21 (104.21-344.02)	109.83 (97.39-122.27)	0.320
Age (years) – median (IQR)						
<80	120.21 (75.18-221.64)	136.67 (108.48-183.82)	0.820	234.52 (188.78-283.65)	211.74 (145.49-303.98)	0.630
≥80	93.38 (73.06-162.05)	160.57 (123.85-205.91)	0.086	152.32 (99.38-257.44)	200.28 (168.81-326.65)	0.070
Body weight (kg) – median (IQR)						
≤60	119.81 (77.20-168.64)	125.50 (81.82-171.67)	0.900	189.89 (124.10-279.20)	172.11 (146.20-251.62)	0.610
>60	97.69 (63.09-259.74)	146.91 (119.40-196.80)	0.220	147.03 (96.66-402.25)	214.86 (154.73-361.76)	0.370
Sex – median (IQR)						
M	120.21 (73.06-170.18)	136.67 (108.83-186.49)	0.220	170.89 (94.56-210.02)	208.62 (147.87-274.47)	0.200
F	116.88 (75.18-168.64)	169.06 (118.17-210.38)	0.200	250.77 (104.21-303.57)	237.40 (165.59-375.28)	0.370

*There are only 2 participants who receive standard-dose apixaban (5 mg oral twice daily), whereas their creatinine clearance is below 30 mL/min (CrCl <30 mL/min). The data about peak and trough concentration should be careful in making decisions.



Apixaban concentrations after dosing in patients receiving 2.5mg twice daily (left) and 5 mg twice daily (right) are shown on this picture. The patients who creatinine clearance is below the level of 50 mg/dL (CrCl <50 mg/dL) are indicated in blue and for the patients who creatinine clearance are above or equal to the level of 50 mg/dL (CrCl ≥50) are indicated in pink. The vertical lines indicate median.

Figure 2 Peak and trough apixaban concentrations in reduced-dose and standard-dose groups with CrCl <50 mL/min and CrCl ≥ mL/min



The blue line is indicated for 2.5 mg apixaban twice daily in reduced-dose group and 5 mg apixaban twice daily in standard-dose group. The shaded orange parallelogram indicates the standard calculated peak and trough concentration for reduced-dose were 69-221 and 34-162 ng/mL, and for standard-dose were 91-321 and 41-230 ng/mL respectively.

Supplemental Figure 2 Peak and trough apixaban concentrations for individual patients in reduced-dose and standard-dose groups

In the level of CrCl ≥50 mL/min, the peak level of apixaban concentration in 20 patients consuming standard-dose had median peak level of 211.74 (151.71-311.30) ng/mL vs 7 patients consuming reduced-dose had median peak level of 89.11 (82.16-210.02) ng/mL (p value = 0.041), and the trough level of apixaban concentration in 20 patients consuming standard-dose had median trough level of 140.50 (108.48-180.17) ng/dL vs 8 patients consuming reduced-dose had median trough level of 82.27 (69.52-129.72) ng/dL (p value = 0.047). The plasma level of apixaban concentration (peak and trough concentration) was significant different between these two groups. The peak and trough concentration of apixaban in patients consuming reduced-dose was significantly lower than standard-dose apixaban while the level of renal function is higher (CrCl ≥50 mL/min).

In other condition, the median peak and trough concentration of apixaban in reduced-dose vs standard-dose group were 152.32 (99.38-257.44) ng/dL and 93.38 (73.06-162.05) vs 200.28 (168.81-326.65) ng/mL and 160.57 (123.84-205.91) ng/mL ng/mL respectively in age ≥80 years. The median peak and trough concentration of apixaban in reduced-dose vs standard-dose group were 189.89 (124.10-279.20) and 119.81 (77.20-168.64) vs 172.11 (146.20-251.62) ng/mL and 125.50 (81.82-171.67) ng/mL ng/mL respectively in body weight ≤60 kg. There were no significant different between these groups. The other specific condition was also shown in Table 3, Figure 3 and Supplement figure 1.

The incidence of hemorrhagic stroke and all cause of bleeding events during first 3 months were shown in Table 4. There was no incidence of recurrent ischemic stroke during first 3 months after receiving apixaban.

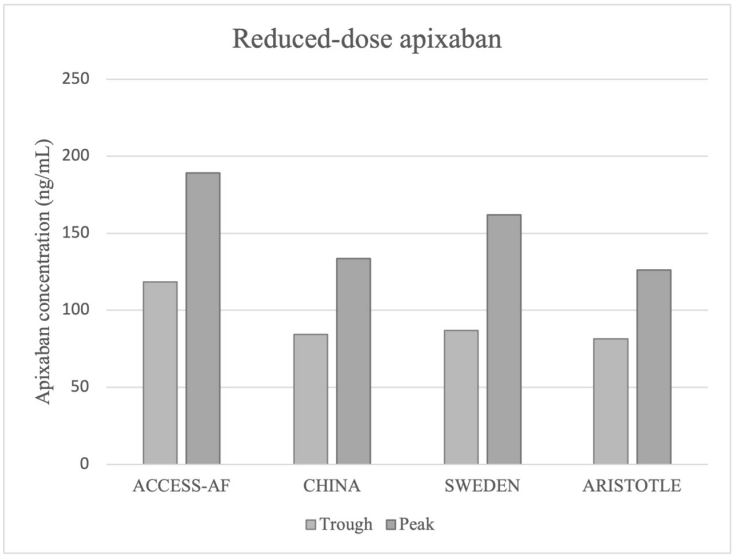
Table 4 Incidence of hemorrhagic stroke and all cause of bleeding events during first 3 months after received apixaban

Outcomes	Reduced-dose apixaban (n = 24)	Standard-dose apixaban (n = 32)
Stroke events		
Hemorrhagic stroke* (%)	N/A	N/A
Odd ration (95%CI)	N/A	
p-value	N/A	
Bleeding events		
Major bleeding[#] – n (%)	3 (12.50%)	4 (12.50%)
Odd ration (95%CI)	1.00 (0.20-4.95)	
p-value	1.00	
Minor bleeding[+] (%)	2 (8.33%)	3 (9.38%)
Odd ration (95%CI)	1.14 (0.17-7.41)	
p-value	0.89	

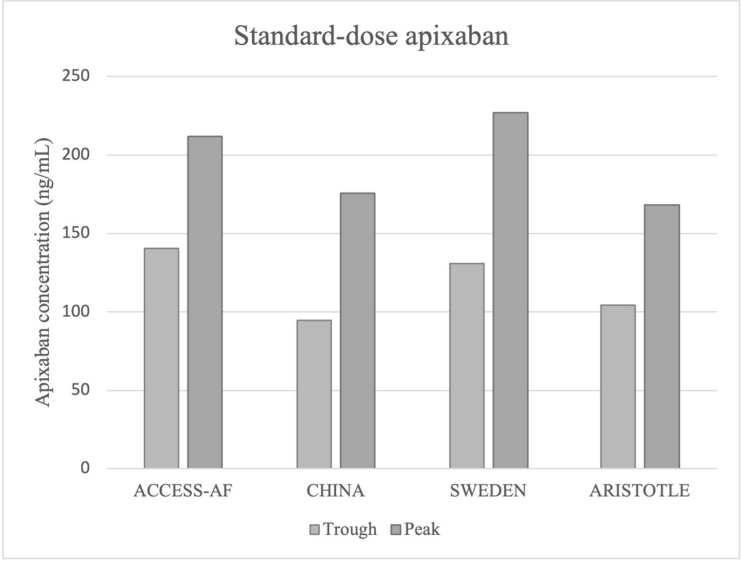
*There is not any participants occur hemorrhagic stroke. However, there was 1 patient occur hemorrhagic transformation by prior using rt-PA before start apixaban rapidly in 48 hours

[#]Major bleeding including to intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), massive upper gastrointestinal bleeding (UGIB), and massive hematuria

[+]Minor bleeding including to minor ecchymosis, minor petechiae, microhematuria, bleeding per gum, and epistaxis



A) Comparison of peak and trough concentrations in reduced-dose apixaban



B) Comparison of peak and trough concentrations in standard-dose apixaban

Figure 3 Comparison of median peak and trough apixaban concentrations between ACCESS-AF study and others

Discussion

In comparison with the ARISTOTLE study[10], apixaban concentration of this study were higher (Figure 3), which the median peak and trough concentration were 211.7 ng/mL and 140.5 ng/mL at 5 mg dose and 189.31 ng/mL and 118.5 ng/mL at 2.5 mg dose respectively. On the contrary, our results were comparable with other real-world studies from China and Sweden.[17,18] Differences of

the results can be probably affected by baseline characteristics of real-world study that populations were older age, lower body weight (especially in Asian patients) and lower renal function.

The ENGAGE AF-TIMI 48 study[9], reported a higher ischemic stroke rate for edoxaban in patients with CrCl >95 mL/min (hazard ratio (HR) [95% confidence interval (CI)]: 1.45 (0.90-2.35); p=0.13). Approximately half of the edoxaban dose is eliminated by the kidney, and edoxaban blood levels are lower in patients with better renal function, averaging about 30% less in patients with CrCl >80 mL/min, and 40% less in patients with CrCl >95 mL/min. The FDA mentioned that "As renal function improves and edoxaban blood levels decrease, the risk for ischemic stroke increases in patients with NVAF".[19] In addition, the European Medicines Agency (EMA) issued the recommendation that "Edoxaban should be used only in patients with high CrCl after careful evaluation of individual thromboembolic and bleeding risk".[20] A nationwide study where patients taking edoxaban 30mg and having a CrCl >95 mL/min presented higher incidence of stroke than warfarin treated patients.[21] This suggests that either the desired therapeutic range is not reached or the drug is more rapidly eliminated. However, there is real-world study that showed no increase in complication rates in patients with CrCl >90 mL/min neither in those treated with edoxaban or in those treated with DOACs.[22]

In this study found the plasma concentration of Apixaban, both peak and through concentrations, in NVAF that had CrCl ≥50 mL/min who received reduced-dose apixaban was significant lower than standard-dose group. However, apixaban concentration was still in expected range in all patients in this study. One patient with CrCl ≥50 mL/min had unexpectedly under dosing and had plasma concentration level at lower border of the expected range (trough concentration 51.0 ng/mL and peak concentration 89.0 ng/mL, (41.0-321.0 ng/mL)]. This information would support the possibility that higher renal function will lead to lower drug concentration even in apixaban that has 27% renal clearance, especially in patient that received reduced-dose apixaban both with and without fulfilled criteria dose reduction. Our findings challenge the current consensus regarding apixaban dosing in patients with NVAF, using reduced-dose apixaban with caution, not only the manufacturer criteria but evaluating creatinine clearance of each patients should be consider.

On the other hand, the plasma concentration of Apixaban, both peak and through concentrations, in NVAF patients that had CrCl <50 mL/min were comparable in both who received reduced-dose and standard-dose apixaban. Also, same findings in all aspects (age, body weight and SCr) that use for adjust apixaban dose. Reflect that follow routine criteria to reduce dose Apixaban, as in this study had 75% fulfilled criteria reducing dose, show satisfied comparable drug level in both reduced-dose and standard-dose groups. However, 2 out of 4 patients with CrCl <50 mL/min in our standard-dose group had peak concentration of apixaban at upper border of expected range and 1 case had extremely high peak level. In the study on the efficacy and safety of off-label dose according to plasma concentration (Michihiro Saua 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.[16] 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, selective serotonin reuptake inhibitor (SSRI) and the others should be closed monitored of bleeding complications.[23] Therefore, peak concentration measurement may be valuable used to improve the risk-benefit ration in this group.

Of patients prescribed apixaban 2.5 mg, 25% of patients in our study did not meet criterial for apixaban adjusted dose. Compared with J Harrington et al., 61% of patients were reduced dose, but not reduced risk. The patients on reduced-dose apixaban did not meet fulfill criterial for adjusted dose. There were more likely to be female and have comorbidities such as heart failure, hypertension and prior ischemic stroke[24]. Similar to our study, we noticed that only 6 patients (25%) did not meet criteria for apixaban dose adjustment. One was 92-year-old male patient and was concern about risk of bleeding. Five were had underlying disease about heart failure and 3 of them had body weight ≤60 kg.

The present study had several limitations. First, it was an observational study conducted in single center. Second, since it was performed in real-world clinical setting, selection bias could not have been avoided. Third, the sample size was not big enough to determine the important of each factors. Finally, the study did not provide the efficacy of apixaban related to drug concentration and follow up outcome duration maybe too short to identify more accurate data. Nonetheless, our pilot study raises the awareness of prescribing reduced-dose apixaban. Further study should focus on CrCl adding to conventional factors and efficacy especially in high renal function patients with reduced-dose apixaban should be monitor.

Conclusion

There was significant difference between peak and trough concentration of reduced-dose apixaban in patients with CrCl ≥50 mL/min. To reduce apixaban dose, not only fulfilled the manufacture recommendation, but also concerning of creatinine clearance is important. The role of concentration measurements to improve clinical outcome with apixaban warrants evaluation.

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