*Article*

# Anti-Factor Xa Activity of Apixaban in Extremely Low Body Weight

Wanwarang Wongcharoen [ID], Amarase Pamarapa, Siriluck Gunaparn [ID] and Arintaya Phrommintikul *[ID]

Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand; bwanwarang@yahoo.com (W.W.); amakawa.mc@gmail.com (A.P.); siriluck.g@cmu.ac.th (S.G.)
* Correspondence: arintaya.p@cmu.ac.th

**Abstract**

**Background:** Direct oral anticoagulants (DOACs) are generally preferred over warfarin for preventing arterial and venous thromboembolism. However, the efficacy and safety of DOACs in patients with extremely low body weight (BW) are uncertain. This study investigates anti-factor Xa (anti-FXa) activity of apixaban and compares it between patients with normal BW (>50 kg) and underweight (≤50 kg). **Methods:** We enrolled 150 patients on branded generic apixaban (Apixan$^{TM}$) for atrial fibrillation (AF), venous thromboembolism, and intracardiac thrombus. Anti-FXa activity of apixaban was measured at peak concentration ($C_{peak}$) and trough concentration ($C_{trough}$) after at least one week of therapy. **Results:** Mean age was $64.0 \pm 12.7$ years, with 53.3% being male. Mean BW was $61.3 \pm 15.3$ kg. Of the 150 patients, 132 (88%) had AF, and 43 (28.7%) had low BW. Overall, 87.3% and 84.7% of patients had $C_{trough}$ and $C_{peak}$ within the expected range. Underweight patients had significantly higher mean $C_{trough}$ and $C_{peak}$ than normal BW patients. A higher proportion of low-BW patients exceeded the expected $C_{peak}$ range compared to normal-BW patients (25.6% vs. 3.7%, $p < 0.001$). Low BW was the only independent predictor of exceeding $C_{peak}$ specified range (adjusted OR 4.87, 95% CI 1.31–18.15, $p = 0.018$). **Conclusions:** Most patients maintained apixaban levels within expected ranges, but those with low BW were more likely to exceed the specified range of $C_{peak}$.

**Keywords:** atrial fibrillation; direct factor Xa inhibitor; coagulation factor Xa; body weight

## 1. Introduction

Atrial fibrillation (AF) poses a significant global health challenge [1,2]. The incidence of AF is rising due to the aging population, leading to complications that adversely affect patients' quality of life, including a five-fold-increased risk of ischemic stroke [3–5]. Over the past decade, direct oral anticoagulants (DOACs) have revolutionized anticoagulation therapy for patients with AF and are now preferred over warfarin [6].

Apixaban, a direct, oral, reversible, and highly selective inhibitor of factor Xa (FXa), has been demonstrated to be superior to warfarin in preventing stroke and systemic embolism. It is associated with a lower incidence of bleeding and reduced mortality in most clinical settings [7]. Prior studies have demonstrated a connection between the use of DOACs in underweight individuals and a heightened risk of major bleeding and mortality from any cause [8,9]. Nevertheless, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial included a small proportion of patients with a body weight (BW) of 50 kg or less [7].

As the Asian population generally has lower BW compared to their Western counterparts, the use of DOACs in this lower BW range requires special caution. Lower BW can result in a reduced volume of distribution and slower drug clearance, potentially leading to unintentional supratherapeutic levels [10]. A pharmacokinetic study of apixaban conducted in 54 healthy subjects demonstrated that individuals weighing $\leq 50$ kg had approximately 27% higher maximum observed plasma concentration and area under the concentration–time curve for apixaban [11]. However, there are currently no specific dose adjustments recommended for these patients.

Consequently, we aimed to assess the anti-FXa activity of apixaban to compare the proportion of patients whose levels fall within the expected range as defined by the European Heart Rhythm Association (EHRA) guidelines [12] between patients with normal BW (>50 kg) and those with extremely low BW ($\leq$50 kg). Additionally, we sought to identify factors associated with anti-FXa activity exceeding the specified range.

## 2. Methods

### 2.1. Study Design

This was a single-center, open-label, prospective cohort study conducted at Maharaj Nakorn Chiang Mai Hospital, a tertiary care university hospital in Chiang Mai, Thailand. Investigators affiliated with Chiang Mai University designed the trial, collected data, and performed all statistical analyses. The study protocol received approval on 28 March 2023 (approval number 107/2023) from the ethics committee of the Faculty of Medicine, Chiang Mai University. The research adhered to the ethical principles of the Declaration of Helsinki, including obtaining written informed consent from all participants. The study is registered with the Thai Clinical Trials Registry (TCTR) at https://www.thaiclinicaltrials.org/ with the identification number TCTR20230410004, date of registration 7 April 2023.

### 2.2. The Studied Population

Adults aged $\geq$20 years with indication (s) for an oral anticoagulant, including clinical AF or atrial flutter (with non-gender $CHA_2DS_2$-VASc score $\geq 1$), intracardiac thrombus, and venous thromboembolism were eligible to participate in the trial. Exclusion criteria included significant mitral stenosis, mechanical heart valve recipients, an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 $m^2$, and advanced chronic liver disease (Child–Turcotte–Pugh B or greater). Additionally, pregnant and breastfeeding women were excluded due to insufficient data on the use of DOACs in these conditions.

### 2.3. Trial Procedures

After obtaining the informed consent, the enrolled patients received Apixan$^{TM}$, a branded generic apixaban manufactured by Intas Pharmaceuticals LTD, Ahmedabad, India. Berlin Pharmaceutical Industry (Bangkok, Thailand) supplied a one-year supply of branded generic apixaban for each participant but was not involved in the trial design or results. Each participant was prescribed either 5 mg or 2.5 mg of branded generic apixaban twice daily, with dose adjustments made according to standard clinical guidelines. All patients receiving apixaban 2.5 mg met at least two of the three criteria of reduced dose. Data on patients' demographics, medical history, and current medications were collected. Blood samples were taken at least 7 days after the first dose of apixaban. These samples were collected in 3.2% sodium citrate tubes at trough and peak timepoints. They were centrifuged at $2500\times g$ for 15 min at room temperature within 30 min of collection. These samples included the trough anti-FXa level, measured 15 min before the next dose of apixaban, and the peak anti-FXa level, measured 2–4 h after dosing. Additionally, complete blood counts, renal function tests, and basic coagulation tests were performed. Medication

adherence was monitored through meticulous pill counts and verification of the exact time each participant took apixaban the previous day. Any patient who did not adhere to the medication regimen was scheduled for laboratory testing at a later date. Follow-up visits were scheduled every 3–4 months at the outpatient clinic to assess for side effects, adverse events, or potential drug discontinuation. Anti-FXa activity was measured using the Biophen$^{TM}$ Heparin Liquid Reagent Technology (LRT) kit, a chromogenic anti-FXa assay from Hyphen BioMed (Neuville-sur-Oise, France). The assay was analyzed with the Sysmex CS-2500 system (Siemens Healthineers, Erlangen, Germany) and converted to apixaban plasma concentration using a commercial apixaban calibrator with a concentration sensitivity ranging from 0 to 700 mcg/L. The chromogenic assay for apixaban-specific anti-FXa activity showed a linear correlation with direct plasma concentration measurements obtained through liquid chromatography–tandem mass spectrometry (LC-MS-MS) [13].

### 2.4. Trial Outcomes

The primary objective of the present study was to evaluate the anti-FXa activity of branded generic apixaban (Apixan$^{TM}$) in clinical practice and to compare apixaban peak ($C_{peak}$) and trough ($C_{trough}$) concentrations between patients with extremely low BW ($\leq$50 kg) and those with normal BW (>50 kg). Additionally, we aimed to assess the proportion of patients exceeding expected therapeutic ranges and identify factors associated with supratherapeutic concentrations.

According to previous studies, the expected plasma concentrations of apixaban 5 mg at trough and peak ranged from 41 to 230 mcg/L and 91 to 321 mcg/L, respectively. For apixaban 2.5 mg, the expected $C_{trough}$ and $C_{peak}$ ranged from 34 to 162 mcg/L and 69 to 221 mcg/L, respectively [12,13].

### 2.5. Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics and the primary outcome. Categorical variables, such as gender, presence of co-morbidities, and indications for oral anticoagulant (OAC) therapy, were presented as frequencies and percentages. Continuous variables, such as age and baseline laboratory results, were presented as means $\pm$ standard deviation. $CHA_2DS_2$-VASc and HAS-BLED scores as well as trough and peak apixaban plasma levels were reported as medians with interquartile ranges (IQR), both overall and by specific groups. The correlation between clinical factors and $C_{peak}$ levels exceeding the expected value was assessed using binary logistic regression, with both univariate and multivariate analyses. Results are presented as odds ratios (OR) with 95% confidence intervals (CI) and corresponding *p*-values. All analyses were carried out by SPSS version 29.0.2.0 (IBM Corporation, Armonk, NY, USA).

## 3. Results

### 3.1. The Study Population

From May 2023 to January 2024, a total of 150 patients were enrolled in the trial (Figure 1). The majority of these patients (88.0%) required an OAC due to AF. The mean age of the entire cohort was 64 $\pm$ 13 years. The median BW was 58 kg (IQR 50–70 kg), with 43 patients (28.7%) weighing 50 kg or less. The mean age was significantly higher in the normal-weight group compared to the underweight group (69.71 $\pm$ 10.44 years vs. 61.74 $\pm$ 12.84 years, *p* < 0.001). Additionally, the proportion of males was higher in the normal-weight group compared to the underweight group (63.6% vs. 27.9%, *p* < 0.001). Creatinine clearance (CrCl) was significantly lower in the normal-weight group compared to underweight group (45.21 $\pm$ 21.60 mL/min vs. 70.34 $\pm$ 38.56 mL/min, *p* < 0.001). Overall, 84.7% of patients received the standard dose of apixaban, with no significant

difference between the normal-weight and underweight groups. There were three (2%) patients receiving a non-dihydropyridine calcium channel blocker (non-DHP CCB), a moderate inhibitor of CYP3A4 and a weak inhibitor of P-glycoprotein. Detailed baseline characteristics of the study population are illustrated in Table 1.
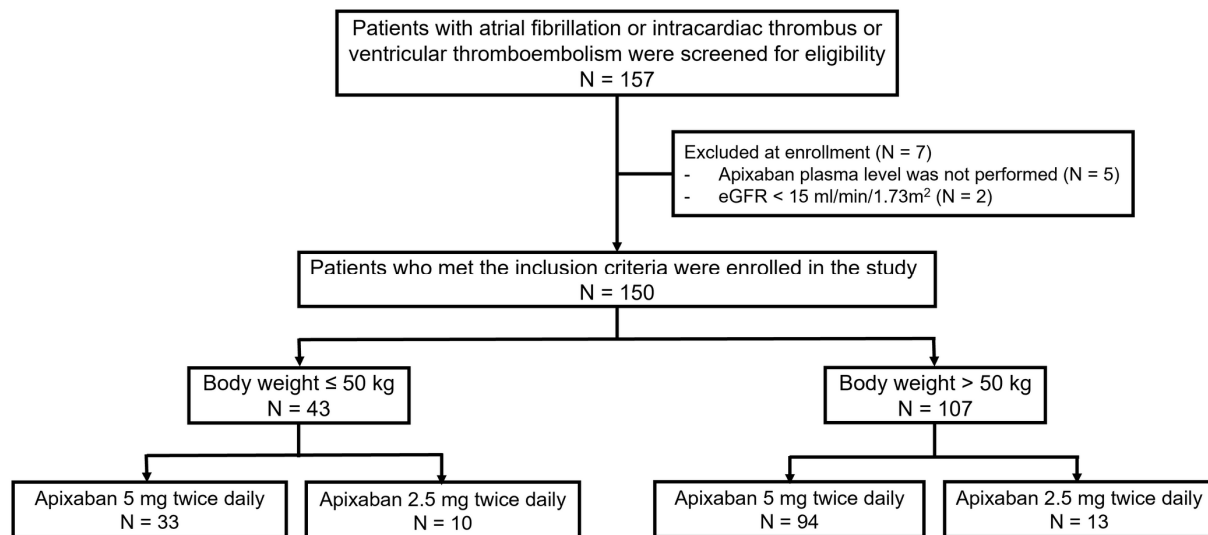


**Figure 1.** Consort flow diagram.

*3.2. The Study Outcomes*

Overall, the median apixaban plasma levels were 101.60 (70.7–134.50) mcg/L and 185.60 (130.80–258.80) mcg/L for $C_{trough}$ and $C_{peak}$ in the standard-dose group and 72.30 (52.80–106.30) mcg/L and 122.30 (94.10–191.90) mcg/L for $C_{trough}$ and $C_{peak}$ in the reduced-dose group, as detailed in Table 2. The $C_{trough}$ and $C_{peak}$ were significantly higher in patients receiving the standard dose compared to those receiving the reduced dose of apixaban. Interestingly, we demonstrated that BW significantly influences plasma apixaban levels for the 5 mg dose but not for the 2.5 mg dose. Patients weighing $\leq$ 50 kg had significantly higher $C_{trough}$ and $C_{peak}$ of apixaban 5 mg compared to those weighing > 50 kg ($p = 0.001$ and $p < 0.001$, respectively). In contrast, for the 2.5 mg dose, there were no significant differences in $C_{trough}$ and $C_{peak}$ between the two body weight groups ($p = 0.074$ and $p = 0.280$, respectively).

In the overall population, 87.3% of patients had their $C_{trough}$ and 84.7% had their $C_{peak}$ within the expected ranges, as shown in Figure 2. However, 3.3% of patients had their $C_{trough}$ and 10.0% had their $C_{peak}$ exceeded the expected ranges. Additionally, four patients (2.7%) had anti-FXa values that exceeded the expected range at both $C_{peak}$ and $C_{trough}$. When comparing patients with normal weight to those with low BW, it was observed that among individuals weighing more than 50 kg, 86.9% of patients had their $C_{trough}$ and 91.6% had their $C_{peak}$ within the expected ranges. In contrast, among patients weighing less than 50 kg, 88.4% of patients had their $C_{trough}$ but only 67.4% had their $C_{peak}$ within the expected ranges. Notably, 25.6% of patients with low BW had their $C_{peak}$ exceeding the expected ranges. None of the underweight patients who received the reduced dose of apixaban had a $C_{peak}$ that exceeded the expected range. However, 5.3% of these patients had a $C_{peak}$ below the expected range. In contrast, 33.3% of the underweight patients who received the standard dose of apixaban had a $C_{peak}$ that exceeded the expected range (Figure 3).

**Table 1.** Characteristics of the Patients at Baseline.

| | Total (n = 150) | Body Weight ≤ 50 kg (n = 43) | Body Weight > 50 kg (n = 107) | p-Value * |
|---|---|---|---|---|
| Age (years) | 64.03 ± 12.69 | 69.71 ± 10.44 | 61.74 ± 12.84 | <0.001 |
| Male (%) | 80 (53.30%) | 12 (27.90%) | 68 (63.6%) | <0.001 |
| Body mass index (kg/m$^2$) | 23.86 ± 4.74 | 19.24 ± 1.78 | 25.73 ± 4.26 | <0.001 |
| Hemoglobin (g/dL) | 12.63 ± 2.06 | 11.57 ± 2.14 | 13.06 ± 1.89 | <0.001 |
| Serum creatinine (mg/dL) | 1.13 ± 0.46 | 1.12 ± 0.44 | 1.14 ± 0.48 | 0.786 |
| CrCl (ml/min) | 63.13 ± 36.32 | 45.21 ± 21.60 | 70.34 ± 38.56 | <0.001 |
| Comorbidities (%) | | | | |
| - Hypertension | 67 (44.70%) | 16 (37.20%) | 51 (47.7%) | 0.279 |
| - Diabetes | 40 (26.70%) | 9 (20.90%) | 31 (29.00%) | 0.415 |
| - Heart failure | 59 (39.30%) | 11 (25.60%) | 48 (44.90%) | 0.041 |
| - CAD | 38 (25.30%) | 17 (39.50%) | 21 (19.60%) | 0.021 |
| - CKD | 19 (12.70%) | 5 (11.60%) | 14 (13.10%) | 1.000 |
| - Stroke | 22 (14.70%) | 4 (9.30%) | 18 (16.80%) | 0.312 |
| OAC indication (%) | | | | |
| - Atrial fibrillation | 132 (88.00%) | 35 (81.40%) | 97 (90.70%) | 0.167 |
| - VTE | 9 (6.00%) | 5 (11.60%) | 4 (3.70%) | |
| - Intracardiac thrombus | 9 (6.00%) | 3 (7.00%) | 6 (5.60%) | |
| Medications (%) | | | | |
| - Beta blocker | 119 (79.30%) | 32 (74.40%) | 87 (81.30%) | 0.376 |
| - DHP CCB | 29 (19.30%) | 7 (16.30%) | 22 (20.60%) | 0.651 |
| - Non-DHP CCB | 3 (2.00%) | 1 (2.30%) | 2 (1.90%) | 1.000 |
| - Amiodarone | 9 (6.00%) | 2 (4.70%) | 7 (6.50%) | 1.000 |
| - Flecainide | 3 (2.00%) | 1 (2.30%) | 2 (1.90%) | 1.000 |
| - Statin | 98 (65.30%) | 25 (58.10%) | 73 (68.20%) | 0.259 |
| Apixaban dose | | | | |
| Apixaban 5 mg twice daily | 127 (84.70%) | 33 (76.70%) | 94 (87.90%) | 0.130 |
| Apixaban 2.5 mg twice daily | 23 (15.30%) | 10 (23.30%) | 13 (12.10%) | |
| CHA$_2$DS$_2$-VASc score Median (Q1, Q3) | 3 (2, 4) | 3 (2, 5) | 3 (2, 4) | 0.106 |
| HAS-BLED score Median (Q1, Q3) | 1 (1, 2) | 2 (1, 3) | 1 (1, 2) | 0.536 |

* Compared between apixaban 5 mg twice daily and 2.5 mg twice daily. CAD = coronary artery disease; CKD = chronic kidney disease; CrCl = creatinine clearance; DHP CCB = dihydropyridine calcium channel blocker; OAC = oral anticoagulant; VTE = venous thromboembolism.

**Table 2.** Trough and peak apixaban plasma level at steady state.

| Apixaban Dosage | Anti-Factor Xa Activity | Total | Body Weight ≤ 50 kg | Body Weight > 50 kg | p-Value * |
|---|---|---|---|---|---|
| Apixaban 5 mg n = 127 | Trough apixaban plasma level (mcg/L) * | 101.60 (70.7–134.50) | 128.30 (104.9–165.00) (n = 33) | 94.85 (65.38–113.75) (n = 94) | 0.001 |
| | Peak apixaban plasma level (mcg/L) * | 185.60 (130.80–258.80) | 258.80 (187.05–350.20) (n = 33) | 163.45 (126.35–228.88) (n = 94) | <0.001 |
| Apixaban 2.5 mg n = 23 | Trough apixaban plasma level (mcg/L) * | 72.30 (52.80–106.30) | 63.75 (47.35–103.20) (n = 10) | 79.10 (66.75–128.50) (n = 13) | 0.074 |
| | Peak apixaban plasma level (mcg/L) * | 122.30 (94.10–191.90) | 123.25 (69.18–172.23) (n = 10) | 122.30 (94.55–195.50) (n = 13) | 0.280 |

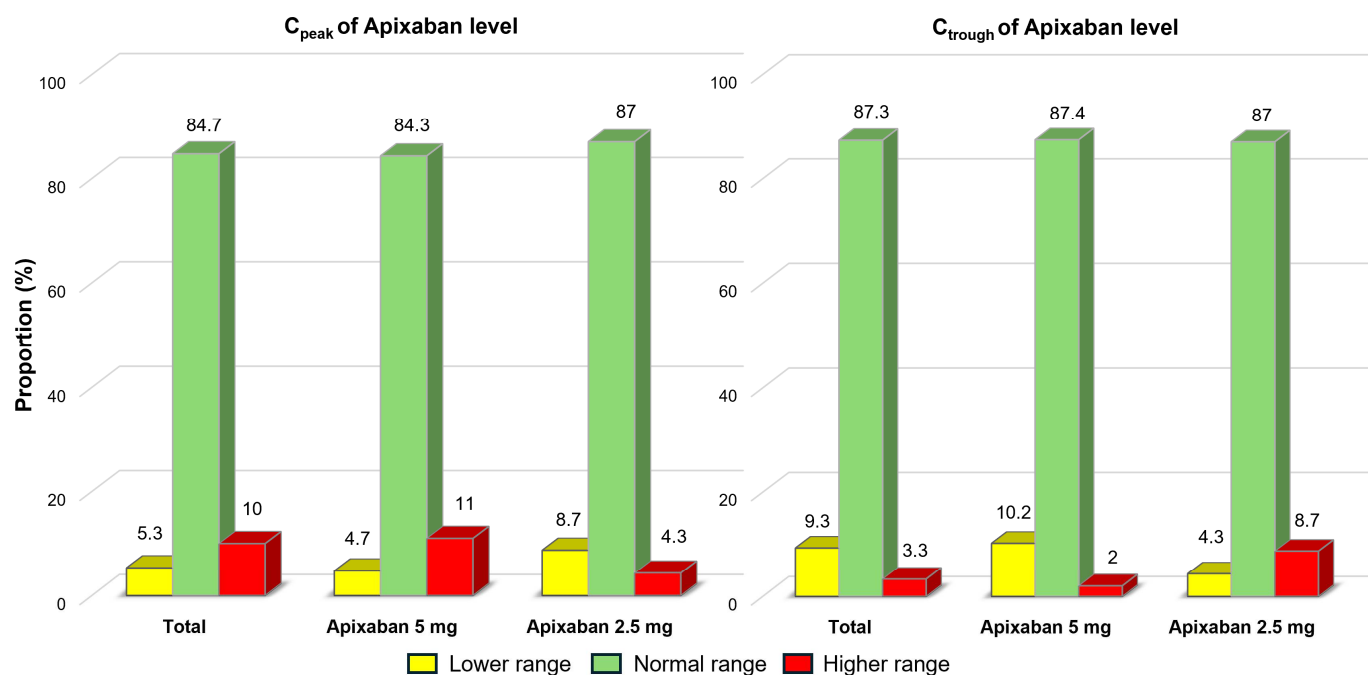* Values are presented as median (Q1–Q3).

**Figure 2.** Proportions of patients with apixaban plasma levels within, below, and above the expected ranges in the entire cohort.
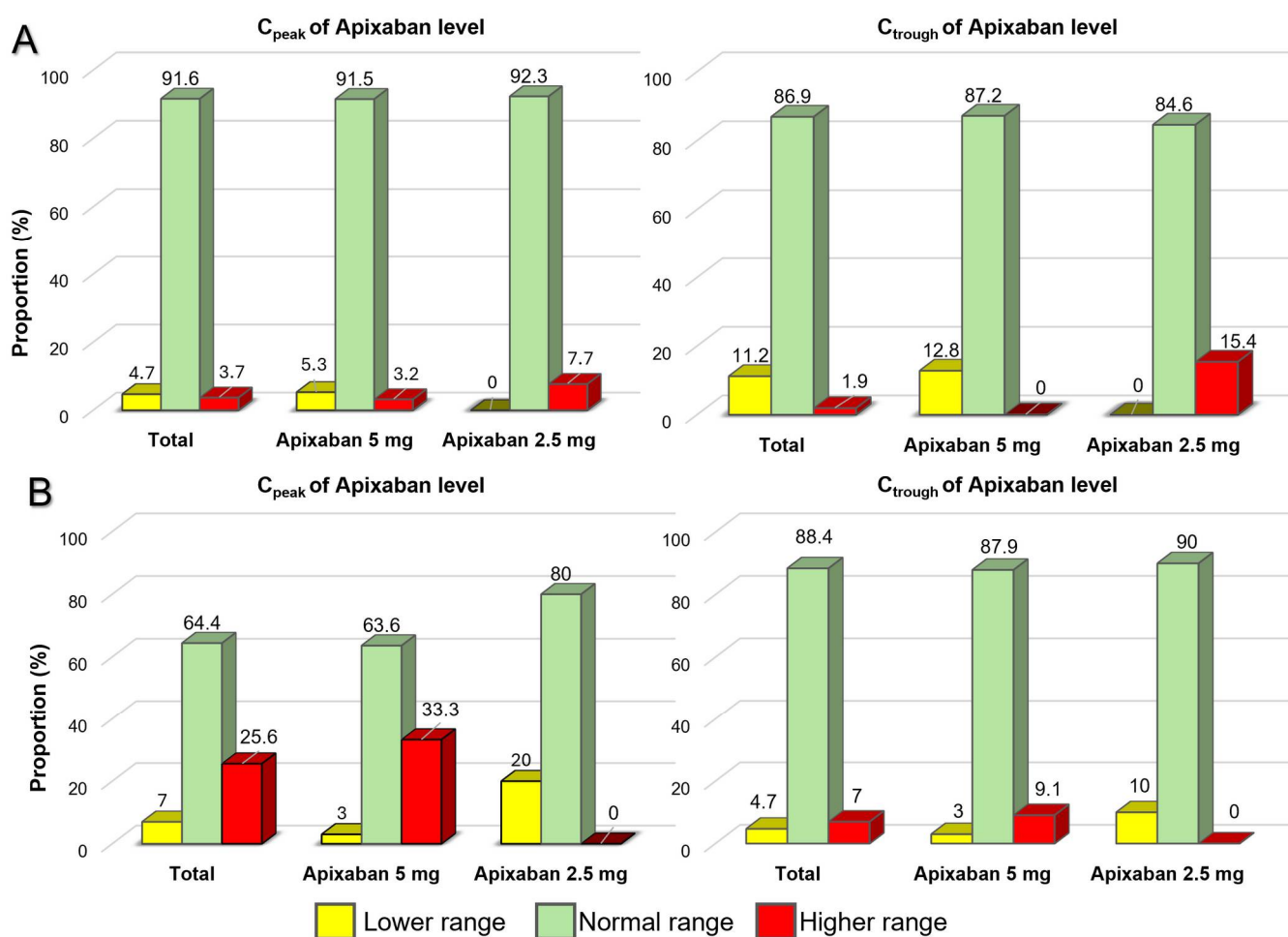


**Figure 3.** Proportions of patients with apixaban plasma levels within, below, and above the expected ranges between those with normal weight (**A**) and those weighing under 50 kg (**B**).

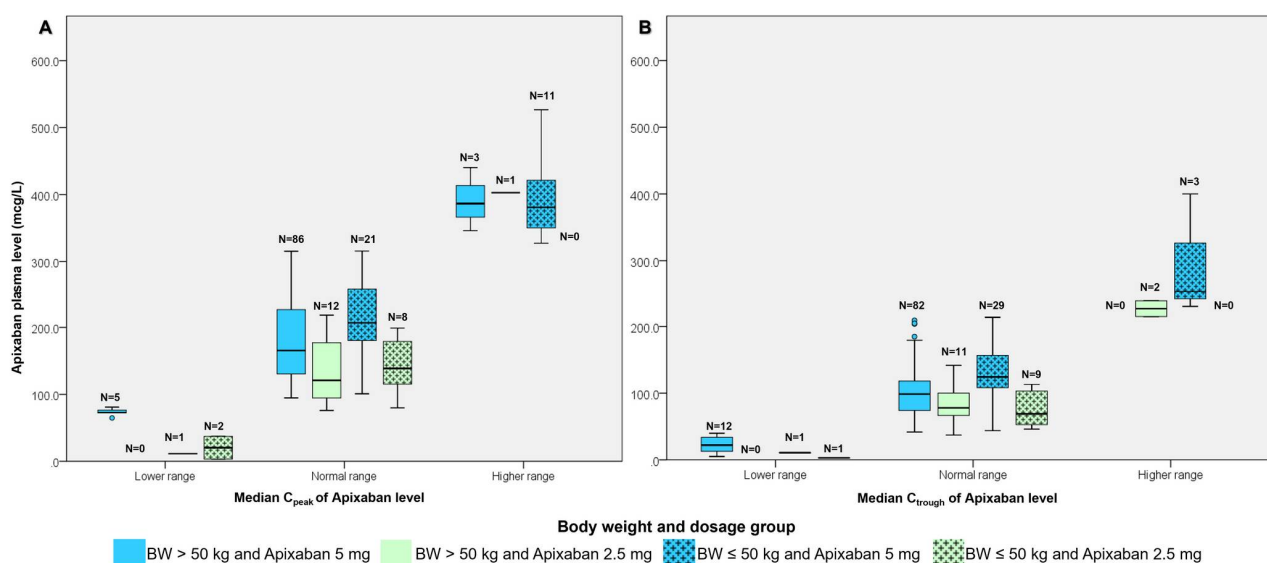Figure 4 illustrate the median $C_{peak}$ and $C_{trough}$ levels stratified by apixaban dose and BW group.



**Figure 4.** Median Cpeak levels (**A**) and median Ctrough levels (**B**) stratified by apixaban dose and body weight group.

The univariate analysis showed that patients weighing $\leq 50$ kg are more likely to have $C_{peak}$ above the expected range (unadjusted OR 8.85, 95%CI 2.63–29.71, $p < 0.001$). While sex and CrCl may influence peak plasma levels of apixaban, these factors were not statistically significant in the multivariate analysis (Table 3). Other variables, such as age, medical history, or concurrent medications, did not show a correlation with $C_{peak}$ levels exceeding the expected range. After adjusting for covariates in the multivariate analysis, low BW was the only independent predictor of exceeding peak concentrations of apixaban (adjusted OR 4.87, 95% CI 1.31–18.15, $p = 0.018$).

**Table 3.** Predictors of peak apixaban plasma level above expected range.

| Predictors | Univariate Analysis Odds Ratio (95% CI) | *p*-Value | Multivariate Analysis Odds Ratio (95% CI) | *p*-Value |
|---|---|---|---|---|
| Female | 5.31 (1.43–19.68) | 0.013 | 3.18 (0.78–12.82) | 0.104 |
| Body weight $\leq 50$ kg | 8.85 (2.63–29.71) | <0.001 | 4.87 (1.31–18.15) | 0.018 |
| Creatinine clearance | 0.97 (0.94–0.99) | 0.033 | 0.98 (0.94–1.03) | 0.563 |

Apixaban was discontinued in eight patients (5.3%). Of these, two patients stopped the medication due to headaches, one due to the progression of chronic kidney disease requiring renal replacement therapy, and another due to the resolution of an intracardiac thrombus. The remaining discontinuations were attributed to personal reasons. During the median follow-up period of $11.0 \pm 2.4$ months, one patient experienced a traumatic intracerebral hemorrhage; however, both $C_{trough}$ and $C_{peak}$ levels were within the expected range for this patient. Additionally, two patients (1.3%) developed ischemic stroke. None of the patients experienced other significant bleeding during the follow-up period.

## 4. Discussion

In this single-center, prospective cohort study of plasma levels of a branded generic apixaban in 150 patients, we found that the majority of patients had their plasma levels

within the expected range and that the drug is relatively well-tolerated. Our results are consistent with previous study on the anti-FXa activity of original apixaban in Thai patients [14]. The lower cost of generic DOACs can lead to their widespread use, improved adherence to treatment regimens, and better overall health outcomes. Our findings may provide reassurance to both healthcare providers and patients regarding the use of generic versions of DOACs.

Previous study has demonstrated that the use of DOAC in underweight patients was associated with the increased risk of major bleeding and all-cause mortality [8,9]. The patients with extremely low BW ($\leq$50 kg) were underrepresented in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, where the median BW of participants was 82 kg [7], much higher than the median BW of 58 kg in our studied population.

Standard clinical practice guidelines for AF do not recommend routine plasma level testing for DOACs [12]. However, several studies have indicated the higher risk of bleeding in patients who have a plasma level of DOAC that exceeds the expected range [14–16]. Importantly, we demonstrated that the extremely low BW was an independent predictor of $C_{peak}$ of apixaban exceeding the expected range. Our findings align with those from previous small studies. Stretton and colleagues reported that 50% of patients with a BW < 50 kg had unexpectedly high levels of DOACs, with the majority using apixaban. However, their study included only 10 patients weighing < 50 kg [17]. Similarly, Wolowiec and colleagues found comparable results, though their study included only seven underweight patients taking apixaban [18]. Several investigators have reported that apixaban has moderate lipophilic properties [19,20]. This increased susceptibility to unexpectedly high levels of apixaban in extremely low BW may be attributed to the reduced accumulation of the drug in adipose tissue and a propensity for higher drug concentrations in the blood.

While higher $C_{peak}$ values in underweight patients are consistent with a reduced volume of distribution, the absence of a similar trend in the 2.5 mg subgroup observed in our study is noteworthy. This could suggest dose-dependent pharmacokinetics, though apixaban is generally described as having linear kinetics within therapeutic doses. Alternatively, variability in adherence, dosing intervals, or metabolism could contribute. Given the small size of the 2.5 mg subgroup, further studies are needed to clarify this observation.

Elevated $C_{peak}$ and $C_{trough}$ values can have important clinical implications for apixaban therapy. An increased $C_{peak}$ may heighten the risk of bleeding due to greater anticoagulant effects [15]. A higher $C_{trough}$ could indicate prolonged drug exposure, potentially leading to drug accumulation and an increased bleeding risk, though it may also enhance thrombotic protection by maintaining consistent anticoagulation [21]. When both $C_{peak}$ and $C_{trough}$ are elevated, overall drug exposure increases, amplifying bleeding risks without necessarily providing additional therapeutic benefits. These findings underscore the importance of therapeutic drug monitoring, especially in populations with low B, or other factors affecting drug metabolism, to optimize safety and efficacy.

Interestingly, no major bleeding events were observed despite 25.6% of low-BW patients having $C_{peak}$ above the expected range. This may reflect that the reference range for $C_{peak}$, as derived from pharmacokinetic studies, is conservative and may not always predict bleeding risk. Our finding aligns with results from the Japanese elderly AF patients (J-ELD AF) registry subanalysis, which found that low BW was not an independent predictor of increased stroke, bleeding, or mortality in elderly Japanese AF patients [22]. This consistency suggests that while pharmacokinetic differences exist, they may not necessarily translate to worse clinical outcomes with on-label apixaban dosing in that specific population. Alternatively, the relatively short observation period and the study's design, which did not focus on bleeding outcomes, may have limited our ability to detect clinically signifi-

cant events. Further longitudinal studies are needed to clarify the relationship between supratherapeutic $C_{peak}$ and bleeding risk, particularly in underweight populations.

The National Institute for Health and Care Excellence (NICE) guidelines for venous thromboembolism recommend monitoring of DOAC level in patients who weigh less than 50 kg [23]. Similarly, the European Heart Rhythm Association (EHRA) guidelines suggest considering the plasma levels of DOACs in patients weighing under 50 kg [12]. Our results align with these recommendations, as extremely low BW was associated with a fivefold increased risk of apixaban levels exceeding the expected range in our study population.

Given our findings and existing guideline recommendations, we propose a practical clinical approach for managing underweight patients on apixaban: (1) initiate standard dose per indication; (2) in patients with BW $\leq$ 50 kg, especially those $\geq$80 years or with impaired renal function, consider measuring anti-FXa levels after steady state is achieved; (3) if $C_{peak}$ exceeds expected range, assess for bleeding risk and consider dose adjustment or more frequent monitoring. This algorithm is intended to guide clinicians in the absence of formal dose-modification recommendations and should be validated in prospective studies.

Our study has several limitations. First, the sample size was relatively small. However, we believe that we enrolled a substantial proportion of patients with extremely low BW, a group often underrepresented in most DOAC studies. Nevertheless, the relatively small number of such patients may limit the statistical power to detect subtle differences in subgroup analyses, particularly in the reduced-dose group. Therefore, findings related to these subgroups should be interpreted with caution. Second, due to the very low incidence of stroke and bleeding events, we were unable to compare the efficacy and safety of apixaban between patients with normal BW and those with extremely low BW. Third, this study was conducted at a single center, which may limit the generalizability of the findings. Regional demographic factors such as age, body composition, and genetic background as well as adherence behaviors may influence apixaban levels and associated anti-FXa activity. Future multi-center studies including more diverse populations are warranted to confirm these results. Fourth, although we collected data on concurrent use of CYP3A4 and P-gp inhibitors, including non-DHP CCBs, the number of patients on these agents was too small to allow for a meaningful subgroup analysis. These patients were included in the overall analysis, which may have contributed to some variability in apixaban levels. This limitation should be considered when interpreting the results, and future studies should further evaluate the impact of drug–drug interactions on apixaban pharmacokinetics.

## 5. Conclusions

The majority of patients exhibited plasma levels within the expected range following administration of apixaban. Importantly, we demonstrated that individuals with extremely low BW were at an elevated risk of having peak anti-FXa activity levels that surpassed the expected range. Caution should be exercised when prescribing apixaban to individuals with extremely low BW.

**Institutional Review Board Statement:** All study procedures involving human participants were conducted in accordance with ethical standards approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (approval number 107/2023 and subsequent amendments; 28 March 2023) or equivalent ethical guidelines. The research protocol adhered to the principles outlined in the ethical principles of the 1964 Declaration of Helsinki. Trial registration: TCTR20230410004 registered in the Thai Clinical Trials Registry (TCTR) https://www.thaiclinicaltrials.org/, date of registration 7 April 2023.

**Informed Consent Statement:** Informed consent was obtained from all individual participants included in the study.

**Data Availability Statement:** The deidentified participant data will be shared on a request-based basis. Please directly contact the corresponding author at arintaya.p@cmu.ac.th and the Faculty of Medicine, Chiang Mai University Ethics Committee to request data sharing.

**Conflicts of Interest:** The branded generic apixaban (APIXAN[TM]) used in this study was provided by Berlin Pharmaceutical Industry Co., Ltd., Bangkok, Thailand. The investigators independently designed and conducted the study; the data were analyzed and the manuscript written by the investigators.

# References

1. Phrommintikul, A.; Detnuntarat, P.; Prasertwitayakij, N.; Wongcharoen, W. Prevalence of atrial fibrillation in Thai elderly. *J. Geriatr. Cardiol.* **2016**, *13*, 270–273.
2. Suwanwela, N.C.; Chutinet, A.; Autjimanon, H.; Ounahachok, T.; Decha-Umphai, C.; Chockchai, S.; Indrabhakti, S.; Kijpaisalratana, N.; Akarathanawat, W.; Travanichakul, S.; et al. Atrial fibrillation prevalence and risk profile from novel community-based screening in Thailand: A prospective multi-centre study. *Int. J. Cardiol. Heart Vasc.* **2021**, *32*, 100709. [CrossRef]
3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch. Intern. Med.* **1994**, *154*, 1449–1457. [CrossRef]
4. Frost, L.; Engholm, G.; Johnsen, S.; Moller, H.; Henneberg, E.W.; Husted, S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch. Intern. Med.* **2001**, *161*, 272–276. [CrossRef] [PubMed]
5. Benjamin, E.J.; Wolf, P.A.; D'Agostino, R.B.; Silbershatz, H.; Kannel, W.B.; Levy, D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation* **1998**, *98*, 946–952. [CrossRef] [PubMed]
6. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.; Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.-A.; E Dilaveris, P.; et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* **2021**, *42*, 373–498.
7. Granger, C.B.; Alexander, J.H.; McMurray, J.J.V.; Lopes, R.D.; Hylek, E.M.; Hanna, M.; Al-Khalidi, H.R.; Ansell, J.; Atar, D.; Ave-zum, A.; et al. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2011**, *365*, 981–992. [CrossRef]
8. Lee, C.-H.; Lin, T.-Y.; Chang, S.-H.; Chen, C.-H.; Hsu, Y.-J.; Hung, K.-C.; Wen, M.-S. Body mass index is an independent predictor of major bleeding in non-valvular atrial fibrillation patients taking dabigatran. *Int. J. Cardiol.* **2017**, *228*, 771–778. [CrossRef]
9. Park, C.S.; Choi, E.K.; Kim, H.M.; Lee, S.R.; Cha, M.J.; Oh, S. Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants. *Heart Rhythm.* **2017**, *14*, 501–507. [CrossRef]
10. Rocca, B.; Fox, K.A.; Ajjan, R.A.; Andreotti, F.; Baigent, C.; Collet, J.P.; Grove, E.L.; Halvorsen, S.; Huber, K.; Morais, J.; et al. Antithrombotic therapy and body mass: An expert position paper of the ESC Working Group on Thrombosis. *Eur. Heart J.* **2018**, *39*, 1672–1686f. [CrossRef]

11. Upreti, V.V.; Wang, J.; Barrett, Y.C.; Byon, W.; Boyd, R.A.; Pursley, J.; LaCreta, F.P.; Frost, C.E. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br. J. Clin. Pharmacol.* **2013**, *76*, 908–916. [CrossRef]

12. Steffel, J.; Collins, R.; Antz, M.; Cornu, P.; Desteghe, L.; Haeusler, K.G.; Oldgren, J.; Reinecke, H.; Roldan-Schilling, V.; Rowell, N.; et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace* **2021**, *23*, 1612–1676. [CrossRef] [PubMed]

13. Byon, W.; Garonzik, S.; Boyd, R.A.; Frost, C.E. Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review. *Clin. Pharmacokinet.* **2019**, *58*, 1265–1279. [CrossRef] [PubMed]

14. Limcharoen, S.; Pongchaidecha, M.; Pimsi, P.; Limprasert, S.; Suphanklang, J.; Saelim, W.; Santimaleeworagun, W.; Boonmuang, P. Do Apixaban Plasma Levels Relate to Bleeding? The Clinical Outcomes and Predictive Factors for Bleeding in Patients with Non-Valvular Atrial Fibrillation. *Biomedicines* **2022**, *10*, 2001. [CrossRef] [PubMed]

15. Suwa, M.; Nohara, Y.; Morii, I.; Kino, M. Safety and Efficacy Re-Evaluation of Edoxaban and Rivaroxaban Dosing with Plasma Concentration Monitoring in Non-Valvular Atrial Fibrillation: With Observations of On-Label and Off-Label Dosing. *Circ. Rep.* **2023**, *5*, 80–89. [CrossRef]

16. Reilly, P.A.; Lehr, T.; Haertter, S.; Connolly, S.J.; Yusuf, S.; Eikelboom, J.W.; Ezekowitz, M.D.; Nehmiz, G.; Wang, S.; Wallentin, L.; et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J. Am. Coll. Cardiol.* **2014**, *63*, 321–328. [CrossRef]

17. Stretton, B.; Kovoor, J.; Bacchi, S.; Gupta, A.; Edwards, S.; Boey, J.P.; Gluck, S.; Reddi, B.; Maddern, G.; Boyd, M. Quantifying time from last dose: Do direct oral anticoagulant assays correlate with patient's reported last dose. *Blood Coagul. Fibrinolysis* **2023**, *34*, 451–455. [CrossRef]

18. Wolowiec, L.; Kusiak, M.; Budzynski, J.; Wolowiec, A.; Jaśniak, A.; Wiciński, M.; Pedrycz-Wieczorska, A.; Rogowicz, D.; Grześk, G. Therapeutic Drug Monitoring of Direct Oral Anticoagulants in Patients with Extremely Low and High Body Weight-Pilot Study. *J. Clin. Med.* **2023**, *12*, 4969. [CrossRef]

19. Martin, K.A.; Lee, C.R.; Farrell, T.M.; Moll, S. Oral Anticoagulant Use After Bariatric Surgery: A Literature Review and Clinical Guidance. *Am. J. Med.* **2017**, *130*, 517–524. [CrossRef]

20. Remko, M. Molecular structure and stability of perindopril erbumine and perindopril L-arginine complexes. *Eur. J. Med. Chem.* **2009**, *44*, 101–108. [CrossRef]

21. Weitz, J.I.; Connolly, S.J.; Patel, I.; Salazar, D.; Rohatgi, S.; Mendell, J.; Kastrissios, H.; Jin, J.; Kunitada, S. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb. Haemost.* **2010**, *104*, 633–641. [CrossRef]

22. Kadosaka, T.; Nagai, T.; Suzuki, S.; Sakuma, I.; Akao, M.; Yamashita, T.; Anzai, T.; Okumura, K.; J-ELDAFinvestigators. Association of Low Body Weight with Clinical Outcomes in Elderly Atrial Fibrillation Patients Receiving Apixaban-J-ELD AF Registry Subanalysis. *Cardiovasc. Drugs Ther.* **2022**, *36*, 691–703. [CrossRef]

23. Schulman, S.; Konstantinides, S.; Hu, Y.; Tang, L.V. Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing: Observations on NICE Guideline [NG158]. *Thromb. Haemost.* **2020**, *120*, 1143–1146. [CrossRef]