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# Factors associated with bleeding outcome of non-vitamin K antagonist oral anticoagulants at a tertiary hospital in Thailand

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## ABSTRACT

This retrospective descriptive study aimed to evaluate the factors influencing bleeding in patients who received non-vitamin K antagonist oral anticoagulants (NOACs) at Phramongkutklao Hospital, Bangkok, Thailand, from January 2015 to February 2019. A total of 416 patients were included in the study. The median age was 73 years, and the median weight was 66.4 kg. NOACs were prescribed for stroke prevention in nonvalvular atrial fibrillation in the majority of the patients. Hypertension, dyslipidemia, and diabetes mellitus were respectively found in 76.2%, 59.9%, and 29.8% of the patients. Among the patients, 126 (30.3%) received dabigatran, 179 (43.0%) received rivaroxaban, 109 (26.2%) received apixaban, and 2 (9.4%) received edoxaban. Bleeding occurred in 39 patients (9.4%), including 22 (5.3%) in the rivaroxaban group, 12 (2.9%) in the dabigatran group, and 5 (1.2%) in the apixaban group. The most common bleeding type was minor bleeding. Age and previous bleeding history were factors that appeared to influence the increased bleeding outcome of NOACs. Therefore, healthcare providers should prescribe NOACs with care and closely monitor bleeding events in the elderly and patients with prior bleeding history.

**Keywords:** direct acting oral anticoagulants; clinical outcome; risk factor; side effect

## 1. INTRODUCTION

In previous years, warfarin was the only anticoagulant prescribed for the treatment and prevention of systemic or cerebral emboli in patients with atrial fibrillation (AF), prosthetic valve replacement, deep vein thrombosis (DVT), and pulmonary embolism (PE) (Ufer, 2005; Witt et al., 2016). However, the limitations of warfarin include a slow onset of action, various genetic polymorphisms, drug interactions with potent herbs and drugs such as vitamin

E, garlic extract, ginseng, CYP450 enzyme inhibitors or inducers. Therefore, the use of warfarin requires a closely monitor of an international normalized ratio (INR) (Ufer, 2005). Today, non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, are approved for thromboembolism prevention in patients with non-valvular AF and various indications (Ingrasciotta et al., 2018). NOACs present major pharmacologic and pharmacokinetic advantages over warfarin, including rapid onset, fewer drug interactions, no need to monitor blood coagulation parameters, and predictable pharmacokinetics. An important pharmacokinetic advantage of nearly all NOACs is that they are renally eliminated. The results of clinical trials have demonstrated the efficacy and safety of NOACs over warfarin for stroke prevention in AF and the treatment and secondary prevention of venous thromboembolism (VTE) (Chan et al., 2018). Specifically, safety profiles revealed that intracranial hemorrhage occurs more frequently in the warfarin group than in the NOACs group (Chan et al., 2018; Sardar et al., 2013). However, bleeding is an important side effect of NOACs that should be of concern to physicians. Several factors, such as old age, low body weight, renal and liver impairments, and drug interactions, could increase bleeding in patients taking NOACs (Bracey et al., 2018). The use of NOACs has rapidly increased over the years, but idarucizumab and andexanet alfa, which are antidotes of NOACs, are not readily available in most hospitals in Thailand. Therefore, closely monitoring and preventing bleeding complications following NOAC treatment is a crucial undertaking. The objective of the present study is to evaluate the factors influencing bleeding during NOAC therapy at Phramongkutklao Hospital, Bangkok, Thailand.

## 2. MATERIALS AND METHODS

This retrospective observational study reviewed the data of patients receiving NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, for various indications at Phramongkutklao Hospital, a tertiary care hospital, between January 2015 and February 2019. The study protocol was approved by the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital (Issue No. Q041h/61_Exp).

### 2.1 Participants

The data were collected from inpatient and outpatient database records at Phramongkutklao Hospital. Patients were eligible for participation in this study if they received NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) to prevent thromboembolism in AF, VTE, and total hip arthroplasty (THA) or total knee arthroplasty (TKA). Patients with dialysis, moderate to severe hepatic impairment, mechanical valve replacement, or moderate to severe mitral valve stenosis or whose necessary data could not be collected were excluded from this work.

### 2.2 Definitions

Bleeding was classified according to the International Society of Thrombosis and Hemostasis (ISTH) guidelines. Major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical site (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular) and/or bleeding, resulting in a decrease in hemoglobin level of over 2 g/dL (1.24 mmol/L) or requiring whole-blood or red-blood cell transfusion of over two units. All other types of bleeding were defined as non-major bleeding (Kaatz et al., 2015; Tomaselli et al., 2017).

### 2.3 Data collection

Electronic medical and paper-based patient records were reviewed to collect clinical data, including age, gender, weight, comorbidities, NOAC indication, NOAC doses, and laboratory data (e.g., serum creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), concomitant drugs, and clinical manifestations of bleeding).

### 2.4 Statistical analysis

The data were managed using Microsoft Excel® and subsequently imported into R program version 3.5.1. for analysis. All variables were analyzed using descriptive statistics to determine the rate of bleeding and percentage of demographic data (e.g., gender, age, weight, comorbidities, indication, and drug-drug interactions). Continuous variables were tested for normality by the Kolmogorov-Smirnov test and then described as the mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). Chi-squared or Fisher's exact test statistics, with an alpha value of $p \leq 0.05$ was selected to determine statistical significance. The 95% confidential intervals (CIs) were calculated. Logistic regression were used to analyze the relationship between various factors (e.g., gender, age, weight, NOAC dose, drug-drug interactions, and renal function) and bleeding outcome.

## 3. RESULTS

Four hundred and twenty-eight patients were retrieved from the computerized hospital database. Twelve patients were excluded due to; age <18 years (3 patients), on dialysis (2 patients with hemodialysis and 2 patients with peritoneal dialysis), valvular AF (3 patients with severe mitral stenosis and 1 patient with mechanical valve replacement at aortic position), and Child-Pugh class B (1 patient) (Figure 1). Therefore, a total of 416 patients with NOACs were enrolled in this study. The median age was 73 years IQR, 65-80 years), and 57.7% of the participants were male. The median weight was 66 kg (IQR, 55-75 kg). The indications of NOACs were nonvalvular AF (91.6%), VTE treatment (4.8%), and thromboembolism prevention in TKA/THA (2.6%). Hypertension (76.2%), dyslipidemia (59.9%), and diabetes mellitus (29.3%) were found. Rivaroxaban, dabigatran, apixaban, and edoxaban were respectively prescribed to 179 (43.0%), 126 (30.3%), 109 (26.2%), and 2 (0.5%) patients. Concomitant drugs known to enhance bleeding included simvastatin (30.1%), verapamil (13.9%), and aspirin (12.8%). Other demographic data are provided in Table 1.

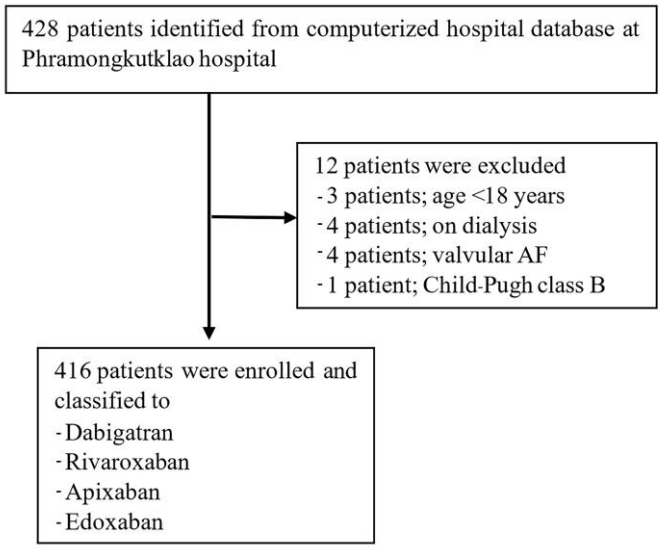


**Figure 1.** Detail of patient flow

**Table 1.** Demographic data of patients who used NOACs (n = 416)

| Demographic data | NOACs | | | | All NOACs |
|---|---|---|---|---|---|
| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban | |
| Gender (n(%)) | | | | | |
| male | 69 (54.8) | 102 (56.9) | 69 (63.3) | 0 | 240 (57.7) |
| female | 57 (45.2) | 77 (43.0) | 40 (36.7) | 2 (100.0) | 176 (42.3) |
| Age (years) (n(%)) | | | | | |
| median | 73 | 71 | 76 | 76 | 73 |
| interquartile | 66-78 | 63-78 | 67-82 | 75-77 | 65-80 |
| Weight (kilograms) (n(%)) | | | | | |
| median | 67 | 65 | 68 | 61 | 66.4 |
| interquartile | 57-75 | 57-76 | 60-75 | 55-68 | 57-75 |
| Co-morbidities (n(%)) | | | | | |
| hypertension | 95 (75.4) | 137 (76.5) | 84 (77.1) | 1 (50.0) | 317 (76.2) |
| diabetes mellitus type 2 | 38 (30.2) | 55 (30.7) | 30 (27.5) | 1 (50.0) | 124 (29.8) |
| dyslipidemia | 73 (97.9) | 115 (64.3) | 65 (59.6) | 1 (50.0) | 254 (59.9) |
| heart failure | 13 (10.3) | 21 (11.7) | 11 (10.1) | 1 (50.0) | 46 (11.1) |
| coronary artery disease | 19 (15.1) | 15 (8.4) | 17 (15.6) | 0 | 51 (12.3) |
| cerebrovascular disease | 55 (43.7) | 31 (17.3) | 27 (24.8) | 0 | 113 (27.2) |
| others | 72 (57.1) | 98 (54.8) | 55 (50.5) | 2 (100) | 227 (54.6) |
| Indication of NOACs (n(%)) | | | | | |
| Non-valvular AF | 121 (96.0) | 151 (84.4) | 106 (97.3) | 2 (100.0) | 381 (91.6) |
| VTE | 2 (1.6) | 2 (1.6) | 18 (10.1) | 4 (3.7) | 24 (5.8) |
| THA | 7(1.7) | 7 (3.9) | 0 | 0 | 7 (1.7) |
| TKA | 4(0.9) | 3 (1.7) | 0 | 0 | 4 (0.9) |
| Use of concomitant drugs (n(%)) | | | | | |
| simvastatin | 44 (34.9) | 51 (28.5) | 30 (27.5) | 0 | 125 (30.1) |
| fenofibrate | 3 (2.4) | 6 (3.4) | 0 | 0 | 9 (2.1) |
| aspirin | 19 (15.1) | 19 (10.6) | 16 (14.7) | 0 | 54 (12.9) |
| clopidogrel | 13 (10.3) | 7 (3.9) | 9 (8.3) | 0 | 29 (6.9) |
| amiodarone | 17 (13.5) | 28 (15.6) | 13 (11.9) | 0 | 58 (13.9) |
| verapamil | 3 (2.4) | 3 (1.7) | 0 | 0 | 6 (1.4) |
| diltiazem | 0 | 4 (2.23) | 2 (1.8) | 0 | 6 (1.4) |

Note: Atrial fibrillation, AF; non-vitamin K antagonist oral anticoagulants, NOACs; venous thromboembolism, VTE; total knee replacement, TKR; total hip replacement, THA; other = chronic kidney disease, chronic obstructive pulmonary disease, myocardial infarction
Dabigatran = 126 patients, rivaroxaban = 179 patients, apixaban = 109 patients, edoxaban = 2 patients

During the study period, overall bleeding events were observed in 39 patients (9.4%) and classified by severity as major bleeding in 6 (1.4%) and minor bleeding in 33 (7.9%). Bleeding was found in 22 (5.3%), 12 (2.9%), and 5 (1.2%) patients who received rivaroxaban, dabigatran, and apixaban, respectively. Most cases of minor bleeding involved epistaxis, gum bleeding, skin bruising, and hemoptysis. The six cases of major bleeding involving GI bleeding (3 patients), intracranial bleeding (1 patient), and hematuria (2 patients). The first case, 78 years old

man received dabigatran 150 mg twice daily for thromboembolism prevention. He has had AF, hypertension, dyslipidemia, and stable angina for more than 10 years and his medications were aspirin, atorvastatin, enalapril, carvedilol and lorazepam. All medications were used at the same dose for a long time. Amiodarone was initiated for rate control management. One month later, he came back to the cardiology outpatient department before the follow up appointment because he had melena. Key laboratory results include a hemoglobin decline to 10.0 g/dL, hematocrit 31.5% (baseline 13.2 g/dL and 3.05%, respectively). Serum creatinine was elevated to 1.5 mg/dL (baseline 1.0 mg/dL). He was diagnosed with GI bleeding and admitted to the hospital. Dabigatran was discontinued and apixaban was initiated when his clinical symptoms were stable. The second case, 82 years old man with known AF, hypertension, chronic kidney disease (CKD) and old cerebrovascular accident (CVA). At the doctor visit, he presented with hematuria. Urinary analysis (UA) showed red blood cells 8 per high-power field. He was taking dabigatran 110 mg twice daily, enalapril, digoxin, bisoprolol and omeprazole for many years. His laboratory data was reported as hemoglobin 9.3 g/dL, hematocrit 28.2% (baseline 11.0 g/dL and 32.8%, respectively) but this visit he was diagnosed with acute kidney injury (AKI). In this case, dabigatran was discontinued. Demographic and characteristics of six patients with major bleeding showed in Table 2. Table 3 demonstrates the bleeding severity according to the ISTH bleeding criteria for each NOACs.

**Table 2.** Demographic and characteristics of six patients with major bleeding from NOACs

| Case | Gender/ Age | PMH | Weight (Kg) | Co-medication | CrCL (mL/min) | Site of bleeding | Management |
|---|---|---|---|---|---|---|---|
| 1 | M/78 | AF, HTN, DLP, stable angina | 70 | Dabigatran 150 mg bid, aspirin, atorvastatin, enalapril, carvedilol and lorazepam | 40.19 | GI bleeding | Discontinued dabigatran and switch to apixaban if clinical stable |
| 2 | M/82 | AF, HTN, CKD, old CVA | 60 | Dabigatran 110 mg bid, enalapril, digoxin, bisoprolol, omeprazole | 29.5# | Hematuria | Discontinued dabigatran |
| 3 | F/78 | AF, HTN, DLP, CKD | 56 | Rivaroxaban 20 mg OD, Losartan, carvedilol, rosuvastatin, omeprazole | 45.2 | GI bleeding | Discontinued rivaroxaban and switch to apixaban if clinical stable |
| 4 | M/65 | AF, HTN, HF, BPH | 50 | Rivaroxaban 15 mg OD, doxazosin, enalapril, metoprolol tartrate, lercanidipine, omeprazole | 38.5 | Intracranial hemorrhage | Discontinued rivaroxaban |
| 5 | F/81 | AF, MI, HF, HTN, CKD, DLP | 45 | Apixaban 2.5 mg bid, enalapril, bisoprolol, atorvastatin, amlodipine, omeprazole | 25# | Hematuria | Discontinued apixaban and restarted if clinical stable |
| 6 | F/82 | AF, HF, HTN, CKD, old CVA, dyspepsia | 50 | Apixaban 2.5 mg bid, enalapril, metoprolol tartrate, atorvastatin, ezetimibe | 52.5 | GI bleeding | Discontinued apixaban and restarted if clinical stable |

Acute kidney injury occurred in this visit

Note: Atrial fibrillation, AF; benign prostatic hyperplasia, BPH; cerebrovascular accident, CVA; chronic kidney disease, CKD; creatinine clearance, CrCL; dyslipidemia, DLP; gastrointestinal, female, F; GI; heart failure, HF; hypertension, HTN; male, M; myocardial infarction, MI

**Table 3.** Bleeding from NOAC therapy classified according ISTH bleeding severity

| TIMI bleeding | NOACs (N=416) | | | |
|---|---|---|---|---|
| | Dabigatran | Rivaroxaban | Apixaban | All NOACs |
| Major | 2 (0.5) | 2 (0.5) | 2 (0.5) | 6 (1.4) |
| Minor | 10 (2.4) | 20 (4.8) | 3 (0.7) | 33 (7.9) |
| Total | 12 (2.9) | 22 (5.3) | 5 (1.2) | 39 (9.4) |

Note: no bleeding in the edoxaban group

Factors associated with bleeding from NOACs are provided in Table 4. Univariate analysis using Fisher's exact test revealed no significant difference in bleeding due to factors such as gender (odds ratio (OR), 0.7; 95% confidence interval (CI), 0.3-1.4; $p = 0.307$), weight (OR, 0.9; 95% CI, 0.5-2.1; $p = 1.000$), drug-drug interaction (OR, 0.8; 95% CI, 0.4-1.7; $p = 0.697$), renal function (OR, 1.2; 95% CI, 0.6-2.6; $p = 0.691$), and liver function (AST: OR, 1.2; 95% CI, 0.4-3.6; $p = 0.754$; ALT: OR, 0.6; 95% CI, 0.1-2.7; $p = 0.531$). Multivariate analyses demonstrated that age (OR, 1.9; 95% CI, 1.0-3.9; $p = 0.047$) and prior bleeding history (OR, 4.9; 95% CI, 2.1-11.1; $p = 0.001$) were factors associated with bleeding from NOACs.

**Table 4.** Factors affecting bleeding from NOAC therapy

| Factors | Bleeding (n=39) | No bleeding (n=377) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Gender (n(%)) | | | | | | |
| male | 26 (66.7) | 214 (56.8) | 0.7 (0.3-1.4) | 0.307 | 1.5 (0.8-3.1) | 0.236 |
| female | 13 (33.3) | 163 (43.2) | | | | |
| Age (years) (n(%)) | | | | | | |
| <75 | 16 (41.0) | 218 (57.8) | 0.5 (0.2-1.0) | 0.065¥ | 1.9 (1.0-3.9) | 0.047** |
| ≥75 | 23 (58.9) | 159 (42.2) | | | | |
| Weight (Kilograms) (n(%)) | | | | | | |
| <60 | 14 (36.8) | 132 (35.6) | 0.9 (0.5-2.1) | 1.000 | 1.1 (0.5-2.1) | 0.877 |
| ≥60 | 24 (63.2) | 239 (54.4) | | | | |
| Drug-drug interactions | | | | | | |
| yes | 22 (56.4) | 195 (51.7) | 0.8 (0.4-1.7) | 0.697 | 1.2 (0.6-2.4) | 0.577 |
| no | 17 (43.6) | 182 (48.3) | | | | |
| Renal function | | | | | | |
| (mL/min/1.73m$^2$) (n(%)) | 14 (35.9) | 153 (40.6) | 1.2 (0.6-2.6) | 0.691 | 0.9 (0.5-1.8) | 0.797 |
| <60 | 25 (64.1) | 224 (59.4) | | | | |
| ≥60 | | | | | | |
| Liver function (U/L) (n(%)) | | | | | | |
| AST<40 | 35(89.74) | 344 (91.3) | 1.2 (0.4-3.6) | 0.754 | 1.2 (0.4-3.6) | 0.754 |
| AST≥40 | 4 (10.26) | 33 (8.8) | | | | |
| ALT<41 | 37(94.87) | 347 (92.0) | 0.6 (0.1-2.7) | 0.531 | 0.6 (0.1-2.7) | 0.531 |
| ALT≥41 | 2 (5.13) | 30 (7.9) | | | | |
| Previous bleeding history | | | | | | |
| yes | 10 (25.6) | 25 (6.6) | 0.2 (0.1-0.5) | <0.001 | 4.9 (2.1-11.1) | <0.001 |
| no | 29 (74.4) | 352 (93.4) | | | | |

Note: *Odds ratio, OR; 95% confidence interval, 95% CI; renal function classified by eGFR (mL/min/1.73 m$^2$)
¥$p$<0.1, analyzed by univariate analysis; **$p$<0.05, analyzed by multivariate analysis

## 4. DISCUSSION

Warfarin has a narrow therapeutic window that can be affected by many factors. Thus, the use of NOACs has become increasingly popular. NOACs have predictable pharmacokinetics and do not require regular laboratory monitoring. The results of landmark clinical studies prove that NOACs cause lower risks of intracranial hemorrhage than warfarin (Connolly et al., 2009; Gómez-Outes et al., 2013; Patel et al., 2011). Bleeding management of patients recieving NOACs depended on severity and cause of bleeding. Although NOACs have specific antidotes, such as idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban, they are not available to all patients (Levy et al., 2018). Practically, blood products including prothrombin concentrate were considered in life-threatening bleeding. Thus, patients with bleeding risk and using NOACs should be closely monitored especially the patients with HAS-BLED score ≥3 points being high risk of bleeding risk (Steffel et al., 2018).

Most data from previous studies show that patients with nonvalvular AF treated with NOACs, except dabigatran (150 mg twice daily) and rivaroxaban (20 mg once daily), are at lower risk of bleeding than those treated with warfarin (Connolly et al., 2009; Patel et al., 2011). This finding is similar to the results of a study from Taiwan, which reported a lower rate of major bleeding in NOACs relative to warfarin (Chan et al., 2018). In a retrospective observational cohort study, Tepper et al. (2018) reported clinically relevant non-major bleeding in 8.5% of the patients in the apixaban group, 10.4% of the patients in the dabigatran group, and 12.4% of the patients in the rivaroxaban group. Major bleeding occurred in 1.4%, 1.5%, and 2.1% of the patients taking apixaban, dabigatran, and rivaroxaban, respectively. In the present study, NOACs were mainly associated with minor bleeding. The rate of major bleeding was fairly similar to that reported by Kijrattanakul and Rojnuckarin (2020), who showed major bleeding events in 1.7% of the patients in the NOAC group (2.2%). The major bleeding events most frequently reported by these authors were gastrointestinal bleeding, intracranial bleeding, retroperitoneal bleeding, and intraarticular bleeding, similar to these results.

Several studies have reported factors that could affect the risk of bleeding when taking NOACs, including age, weight, renal and liver functions, drug-drug interactions, and prior bleeding history (Cheung and Leung, 2017).

The present study confirmed that older age significantly affects the occurrence of bleeding. Hemorrhage occurs more frequently in the elderly (>75 years) than in patients who are under 75 years of age (Hughes and Lip, 2007; Sellers and Newby, 2011). A study by Hughes and Lip (2007) demonstrated a similar trend, that is, patients older than 75 years are more likely to have bleeding complications than patients younger than 75 years (OR, 6.6; 95% CI, 1.2-37; $p$ = 0.032). Hence, the results of the present study are consistent with the previous reports. The bleeding risk associated with NOAC therapy has led physicians to become cautious about prescribing NOACs to elderly patients. The pharmacokinetic data clearly revealed increase in the maximum concentration and area under the curve of NOACs in elderly patients. Decrease in liver and kidney functions, as well as concomitant medications, especially antiplatelet and non-steroidal anti-inflammatory drugs, are relevant factors in these patients (Granger et al., 2011; Kundu et al., 2016).

Prior bleeding history, particularly the occurrence of upper gastrointestinal bleeding from warfarin, had a significant effect on bleeding from NOACs. A systematic review by Hughes and Lip (2007) revealed that a history

of bleeding significantly increases anticoagulant-related bleeding complications (relative risk, 2.40; 95% CI, 1.71-3.38), similar to the findings in this study.

In the present study, six factors, namely, gender, weight, drug-drug interactions, drug dose, renal function, and liver function, did not significantly affect bleeding events. The results of gender and weight were consistent with the findings of subgroup analyses in previous studies (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011). A systematic review by Hughes and Lip (2007) also revealed no difference in bleeding among genders. However, practice guidelines recommended adjusting the doses of dabigatran, apixaban, and edoxaban according to patients' weight (Steffel et al., 2018).

The drugs commonly used with NOACs include aspirin, clopidogrel, simvastatin, fenofibrate, amiodarone, verapamil, diltiazem, and aspirin. While the differences observed were not statistically significant; these medications could increase the risk of bleeding. Aspirin and clopidogrel are antiplatelets and can increase bleeding risk if they are combined with NOACs (Serebruany et al., 2004). Simvastatin, amiodarone, verapamil, and diltiazem can inhibit the p-glycoprotein (P-gp) efflux pump, and all NOACs are P-gp substrates. However, many patients must receive NOACs concomitantly with these drugs (Forbes and Polasek, 2017; Steffel et al., 2018). Unfortunately, this study was not designed to measure the clinical outcomes of drug-drug interactions. Interestingly, in Table 2, the first case with dabigatran treatment had major bleeding. We hypothesized that amiodarone may be a cause of bleeding because amiodarone is a strong P-gp inhibitor. A previous report showed that amiodarone can increase dabigatran plasma level approximately 12-60% (Steffel et al., 2018). Therefore, therapeutic drug monitoring of dabigatran level is necessary for this case. In addition, case number 3 indicated that high BP was the major cause for intracranial hemorrhage. This result was the outcome from the study of Akiyama et al (2015). Therefore, uncontrolled blood pressure is an important risk factor for intracerebral hemorrhage.

According to the 2018 European Society of Cardiology guidelines, the liver and renal functions of AF patients should be assessed before initiating NOAC therapy (Steffel et al., 2018). All NOACs are excreted renally, and dabigatran, followed by edoxaban, rivaroxaban, and apixaban, and shows significant renal clearance. The liver is the major organ in which drugs, especially rivaroxaban, are metabolized. Most of the patients in this study received appropriate NOAC doses according to each drug indication, renal function, and weight. This study presents some limitations that may affect the interpretation of the results. First, we did not have complete data to evaluate the severity of liver disease using Child-Pugh scores. Hence, the liver function of the patients was assessed using blood tests for AST, ALT, total bilirubin, and direct bilirubin. Previous studies on the effects of liver function on bleeding events are limited. Second, some data, such as patients' adherence to medications and history of alcohol use, were not available; the lack of these data may affect the results of this study.

## 5. CONCLUSION

The present study showed that the risk factors associated with bleeding from NOAC therapy include a history of bleeding before taking NOACs and old age. Hence, healthcare providers should prescribe NOACs with care and closely monitor bleeding events in the elderly and patients with previous bleeding history. Moreover, other factors including renal impairment, drug-drug interaction, and low body weight should be concerned.

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