Original Article

Rate of Anticoagulant Use in Patients with Non-Valvular Atrial Fibrillation with and Without History of Major Bleeding

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Background: Anticoagulants can reduce thromboembolic events in patients with non-valvular atrial fibrillation (AF). The underuse of anticoagulant may be related to history of major bleeding.

Objective: To compare the rate of anticoagulant use in non-valvular AF patients with and without a history of major bleeding.

Materials and Methods: The present study was a prospective study of non-valvular AF patients at the cardiology outpatient department of Siriraj Hospital between June 2014 and September 2016. The following data were collected, patient age, gender, underlying disease, risk score, consisting of $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED, history of bleeding and severity, and type of antithrombotic drugs. The rates of anticoagulant use were compared between patients with and without a history of major bleeding.

Results: The authors enrolled 424 non-valvular AF patients, of which 58.7% were male. The mean age was 70.5±10.5 years old. The mean CHA_2DS_2-VASc and HAS-BLED scores were 3.55±1.76 and 1.88±1.05, respectively. Overall, 334 patients (78.8%) received anticoagulants, 75 patients (17.7%) received antiplatelets without an anticoagulant, and 15 patients (3.5%) did not receive any antithrombotic drugs. Of the 424 non-valvular AF patients, 97 patients (22.9%) had a history of bleeding, of which 37 patients (8.7%) had major bleeding. Anticoagulants were used in 67.6% of patients with a history of major bleeding and 79.9% of patients without a history of major bleeding (p=0.08). Patients with a history of major bleeding used warfarin less than those without a history of major bleeding (62.2% versus 77.3%, p=0.040).

Conclusion: Rate of anticoagulant use was 78.7% in patients with non-valvular AF. Patients with a history of major bleeding tended to use warfarin less than those without a history of major bleeding.

Keywords: Atrial fibrillation, Major bleeding, Anticoagulants

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Atrial fibrillation (AF) is a common cardiovascular disease that is responsible for 15% of ischemic strokes and confers sufferers approximately five times higher risk of ischemic stroke compared to the general population[1]. International guidelines recommend the use of anticoagulants in non-valvular AF patients who are at risk[2,3]. Although warfarin can decrease thromboembolic events by two-thirds in patients with non-valvular AF, its underuse is common in clinical practice, especially in Asia, including Thailand[4-8]. Although non vitamin-K-antagonist oral anticoagulants (NOACs) have benefits over warfarin, such as a lower rate of intracerebral hemorrhage and major bleeding[9], warfarin is still the most commonly used anticoagulant in Thailand[10] due to its lower medication cost. One of the important reasons for the suboptimal use of anticoagulants is a bleeding concern by physicians[11], especially since it has been shown that Asian populations have a significantly higher rate of major bleeding, including intracerebral

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hemorrhage, compared to Caucasians[12,13]. A recent study reported that a history of major bleeding is a strong risk factor for future bleeding and patients with previous bleeding are less likely to receive anticoagulants[11].

Since anticoagulants, which can increase the risk of major bleeding, are usually indicated for most patients with non-valvular AF, the purpose of the present study was to determine the rate of anticoagulant use in non-valvular AF patients with and without a history of major bleeding.

Materials and Methods

Study design and population

The present study was a cross-sectional study of non-valvular AF patients 18 years or older who had visited the cardiology outpatient department (OPD) of Siriraj Hospital between June 2014 and September 2016. The study protocol was approved by the Institutional Review Board (IRB) of Siriraj Hospital. All patients gave written informed consent patients were excluded if they had an ischemic stroke in the last three months, a prosthetic heart valve, rheumatic mitral valve disease or significant valvular disease, thrombocytopenia (platelet count of less than 100,000/mm^3) or myeloproliferative disorder, hyperviscosity syndrome, AF with a reversible cause or AF that can be detected only by an implanted device, or a life expectancy of less than three years. Baseline characteristics were collected from history taking and review of medical record, including patient age, gender, underlying disease, risk scores, consisting of CHA_2DS_2-VASc and HAS-BLED, history of bleeding and severity, including duration from date of bleeding to date of enrollment, type of antithrombotic drugs, prothrombin time, and international normalized ratio (INR)[14,15]. Each component of the CHA_2DS_2-VASc score was as follows, C=congestive heart failure (1 point), H=hypertension (1 point), A=age older than 75 years old (2 points), D=diabetes (1 point), S=stroke (2 points), V=vascular disease (1 point), A=age 65 to 74 years old (1 point), and Sc=female sex category (1 point). Each component of the HAS-BLED score was as follows, uncontrolled hypertension, abnormal renal or liver function, history of stroke, history of bleeding, labile INR, elderly (older than 65 years old), and drugs or alcohol usage (1 point each).

Main outcome measurements in the present study were bleeding and use of oral anticoagulation (OAC), which was assess by the review of medical record. Bleeding was classified into major bleeding and minor bleeding. Major bleeding was defined as intracranial hemorrhage, intraspinal hemorrhage, intraarticular hemorrhage, intraocular or retinal hemorrhage, or intramuscular hemorrhage with compartment syndrome, or any bleeding leading to hemoglobin falling by 2 gm/dL or more from the baseline. Minor bleeding was defined as other bleeding that did not fulfill the criteria to be classed as major bleeding.

Sample size calculation was based on the data on the rate of OAC use in patients with and without history of bleeding. Assuming unmatched case and control ratio of 1:4, power 90%, alpha 0.05, the sample sized required for the present study was 420.

Statistical analysis

The categorical variables were reported in frequency and percent. The continuous variables were reported in mean and standard deviation (SD). Chi-square test or Fisher's exact test was used to compare categorical data. Missing data of baseline variables were not allowed in the web-based system. The student's t-test for unpaired data was used to compare continuous data between the two groups (with and without history of major bleeding). The p-value was considered significant if it was less than 0.05.

Results

Between June 2014 and September 2016, the authors enrolled 424 non-valvular AF patients on the present study, of which 58.7% were male. The mean age was 70.5±10.5 years old. Most patients had hypertension (81.1%), one-third had diabetes, and two-thirds had dyslipidemia. The mean CHA_2DS_2-VASc score was 3.55±1.76 and HAS-BLED score was 1.88±1.05. The patients' baseline characteristics are shown in Table 1.

Of the 424 non-valvular AF patients, 97 (22.9%) had a history of previous bleeding, of which 37 (8.7%) involved major bleeding, and 60 (16.2%) minor bleeding (Figure 1). The baseline characteristics of the patients with and without a history of major bleeding are shown in Table 1. Patients with a history of major bleeding were older than and more likely to have a history of stroke or TIA compared to those without a history of major bleeding. Patients with a history of major bleeding had higher CHA_2DS_2-VASc and HAS-BLED scores compared to those without a history of major bleeding.

Rate of oral anticoagulant use

Figure 2 demonstrates the rate of use of different antithrombotic regimens. The rate of warfarin use

Table 1. Baseline characteristic of all non-valvular AF patients classified by history of major bleeding

	All (n=424) n (%)	With history of major bleeding (n=37) n (%)	Without history of major bleeding (n=387) n (%)	p-value
Age (year); mean±SD	70.6±10.6	74.7±8.6	70.2±10.6	0.012
Sex: male	249 (58.7)	26 (70.3)	22.3 (57.6)	0.135
BMI (kg/m^2); mean±SD	25.6±4.5	24.7±4.3	25.6±4.6	0.250
Hypertension	344 (81.1)	34 (91.9)	310 (80.1)	0.080
Diabetes	141 (33.3)	17 (45.9)	124 (32.0)	0.086
Dyslipidemia	285 (67.2)	30 (81.1)	255 (65.9)	0.060
Smoker	139 (32.8)	13 (35.1)	126 (32.6)	0.750
Heart failure	100 (23.6)	7 (18.9)	93 (24.0)	0.484
Implanted cardiac device	93 (21.9)	7 (18.9)	86 (22.2)	0.643
Ischemic stroke or TIA	98 (23.1)	18 (48.6)	80 (20.7)	<0.001
CAD	97 (22.9)	9 (24.3)	88 (22.7)	0.826
CHA_2DS_2-VASc score; mean±SD	3.6±1.8	4.5±1.8	3.5±1.7	0.001
HAS-BLED score; mean±SD	1.9±1.0	2.8±1.14	1.8±1.0	<0.001

SD=standard deviation; BMI=body mass index; TIA=transient ischemic attack; CAD=coronary artery disease

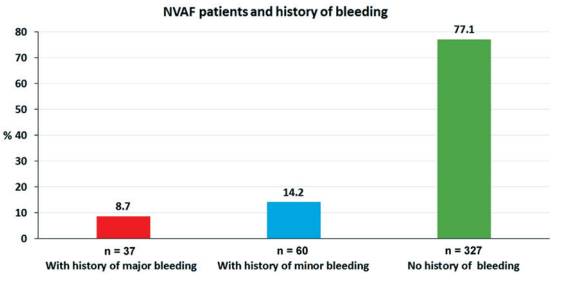

Figure 1. Number of patients categorized by a history of bleeding.

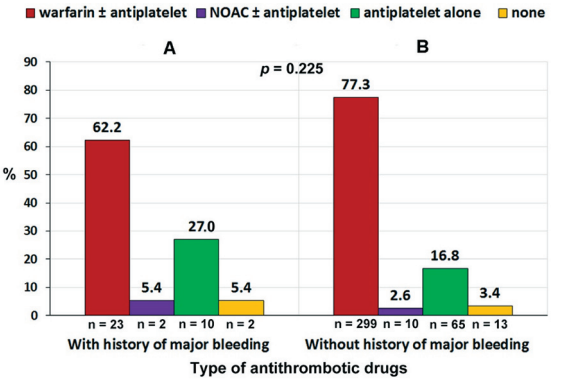

Figure 2. Types of antithrombotic drugs taken by non-valvular AF patients.

in patients with a history of major bleeding was significantly lower than those without a history of major bleeding (62.2% versus 77.3%, p=0.040). When

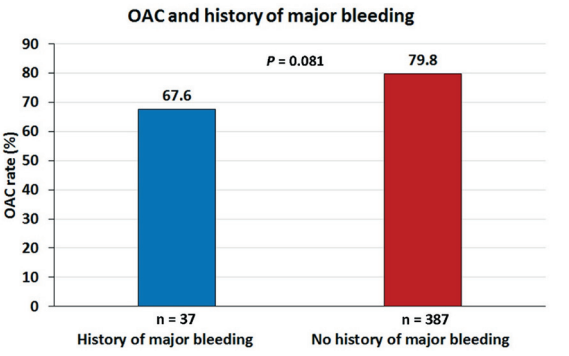

Figure 3. OAC rate comparison between groups with and without a history of major bleeding.

NOAC was included, anticoagulants were used by 334 patients overall (78.7%): 67.6% of patients with a history of major bleeding, and 79.9% of patients without a history of major bleeding (p=0.081) (Figure 3).

Discussion

The present study showed that, among patients with non-valvular AF, 78.7% received anticoagulants and 8.7% of these had a history of major bleeding. The rate of warfarin use in patients with a history of major bleeding was lower than those without a history of major bleeding.

The present result was related with recent international guideline recommendations, which suggest that a bleeding risk should not be the reason for withholding anticoagulants for patients at risk

of stroke[2,3,16]. Current guidelines suggest that the assessment of the risk of bleeding by HAS-BLED score is not for prohibiting the use of anticoagulants but to attempt to control the factors that might promote bleeding[3]. Currently, many countries in Asia, including Thailand, confront the problem of underuse of anticoagulants in patients with AF. One of the important factors to consider is that physicians tend to overestimate the risk of bleeding and underestimate the risk of stroke[17]. One reason for the underuse of anticoagulants may be related to data from previous reports suggesting that Asian populations have approximately four times higher risk of intracranial hemorrhage compared to Caucasians[12]. According to De Caterina et al[11], who evaluated patient outcomes in relation of a history of bleeding and treatment with warfarin or apixaban, clinically relevant or spontaneous bleeding associated with major bleeding or clinically relevant non-major bleeding was not associated with intracranial bleeding, hemorrhagic stroke, or death, thus, encouraging the use of anticoagulants in non-valvular AF patients, even in those with a history of bleeding. However, the present study showed that the rate of warfarin use was still lower in patients with a history of major bleeding.

The proportion of patients with a history of major bleeding in the present study was 8.7%, which is significantly higher than that reported in previous publications[18]. In the Euro Heart Survey study, 61 out of 3,963 patients had a history of major bleeding, which was approximately 1.5% of the study population[18]. Data from the GARFIELD global AF registry showed that among 17,162 patients with non-valvular AF, 2.9% had a history of bleeding[19]. The proportions of patients with a history of major bleeding in Asian populations, such as in the FUSHIMI registry from Japan, seem to be higher (4.2%)[20]. These findings concur with the results from many clinical studies that have reported a higher rate of major bleeding in Asian populations compared to Caucasians, especially when the patients were on warfarin[13]. The Asia-Pacific Heart Rhythm Society guideline emphasizes the benefit of using NOACs in Asian populations to reduce the risk of major bleeding[21]. Many physicians in Asian countries are reluctant to use warfarin for stroke prevention in AF due to the fear of bleeding[22]. The present study findings also confirmed that the rate of warfarin use was lower in patients with a history of major bleeding.

It has been shown that a history of major bleeding increases the risk of future events in patients with coronary artery disease[23] and for patients with AF[11]. Major bleeding is one of the key factors in many bleeding risk scoring systems, such as ATRIA[24], HEMORR$_2$HAGES[25], and HAS-BLED[18]. These results may warn the physicians to consider more carefully the proper treatment for patients in this group regardless of the status of their anticoagulant use. This finding underscores the importance of taking the history of major bleeding in patients with AF and exploring the factors that might be controlled to minimize the future risk.

It has been proposed that the SAMe-TT2R2 score may be a good predictor of suboptimal INR control[26] and might be used to select those who might be suitable for warfarin therapy for stroke prevention. Component factors include female gender, younger than 60 years, medical history i.e., hypertension, diabetes, coronary artery disease, peripheral arterial disease, heart failure, stroke, pulmonary disease, hepatic, and renal disease, interacting drugs, use of tobacco, and race (non-white)[26]. This scoring system has been implemented in some management guidelines for patients with AF[21,27]. However, some experts have commented that the score has a low C-statistics and may not be ready to be used in clinical practice[28].

The present study has several limitations. First, the results of the present study were provided by observations, and therefore, some confounding factors could not be avoided. However, investigators tried to select the variables with minimal bias. Second, the present study patients were mainly enrolled at a cardiology OPD, which cannot be implied to cover all non-valvular AF patients attended to non-cardiology clinic, and thus the OAC-receiving rate may be lower than the present study results. Third, OAC used in the present study was based on the information on the baseline visit. Therefore, changes in OAC strategy was not included in the analysis.

Conclusion

From the present study, non-valvular AF patients received anticoagulants up to 78.7% of cases and 8.7% of these had a history of major bleeding. The rate of warfarin use was lower in patients with a history of major bleeding.

What is already known on this topic?

OACs are indicated in patients with non-valvular AF with risk factors for ischemic stroke. Such medications can increase the risk of major bleeding. Patients with a history of major bleeding have an increased risk of future cardiovascular and bleeding events.

What this study adds?

The proportion of patients with a history of major bleeding in the present study cohort was 8.7%, which is significantly higher than previously reported in Caucasians and even in other Asian populations. The rate of warfarin use was lower in patients with history of major bleeding, reflecting the unmet needs in stroke prevention management in patients with AF.

Conflicts of interest

The authors declare no conflict of interest.

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