History of major bleeding predicts risk of clinical outcome of patients with atrial fibrillation: results from the COOL-AF registry

Rungroj Krittayaphong1,#, Arjborid Winijkul1, Wattana Wongtheptien2, Chaiyasith Wongvipaporn3, Treechada Wisaratapong4, Rapeephon Kunjara-Na-Ayudhya5, Smonporn Boonyaratvej6, Pontawee Kaewcomdee1, Ahthit Yindeengam7, for the COOL-AF Investigators

1Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
2Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand
3Srinakarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
4Faculty of Medicine, Prince of Songkla University, Songkla, Thailand
5Vichaiyut Hospital and Medical Center, Bangkok, Thailand
6Faculty of Medicine, Chulalongkorn University, Songkla, Thailand
7Her Majesty Cardiac Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract

Objective To compare clinical outcomes between patients with and without history of major bleeding according to types of antithrombotic medications in patients with non-valvular atrial fibrillation (NVAF). Methods We conducted a multicenter registry of patients with NVAF during 2014 to 2017 in Thailand. The following data were collected: demographic data, type of NVAF, medical illness, components of CHA2DS2-VASc and HAS-BLED scores, history of bleeding and severity, investigations, and antithrombotic medications. Clinical outcomes were death, bleeding, and ischemic stroke/transient ischemic attack (TIA). Results There were a total of 3218 patients. The average age was 67.3 ± 11.3 years, and 58.3% were men. Sixty-nine patients (2.14%) had a history of major bleeding. Antithrombotic use was, as follows: 2126 patients (75.3%) received oral anticoagulant (OAC) alone, 555 (17.2%) received antiplatelet alone, 298 (9.3%) received both, and 239 (7.4%) received neither. During follow-up, 9.9% had major adverse outcomes, including death (5.9%), ischemic stroke/TIA (2.5%), and major bleeding (4.0%). There were no significant differences in the types of antithrombotic medications between patients with and without history of major bleeding. Multivariate analysis revealed old age, low body mass index, hypertension, diabetes, heart failure, and history of major bleeding to be independently associated with major adverse outcome. Adverse events significantly increased in patients with OAC plus antiplatelet. Conclusions History of major bleeding was identified as a factor that significantly affects clinical outcome. Inappropriate use of OAC plus antiplatelet should be avoided. Special caution should be made in this high-risk patients.

Keywords: Anticoagulants; Atrial fibrillation; Major bleeding; Outcomes

1 Introduction

Non-valvular atrial fibrillation (NVAF) is a common condition, especially in elderly population.1 Ischemic stroke is a major complication of NVAF.2 CHA2DS2-VASc score has been recommended to risk stratify patients with NVAF.3,4 Oral anticoagulant (OAC) therapy are recommended in a majority of patients with NVAF to prevent thromboembolic complication.4 Major bleeding is the most common OAC-related complication. The most fearful site of major bleeding is intracranial bleeding.5,6 This is especially important in Asian population since it has been reported that Asian population had a four-fold risk of intracerebral hemorrhage related to warfarin use compared to Caucasians.7 Although history of bleeding predicts future bleeding episodes in patients who are on OAC, the benefit of taking OAC outweighs the risk in those with NVAF that have additional risk factors.8 HAS-BLED score has been proposed as the bleeding risk assessment tool.9 OAC has been proven to have benefit in stroke prevention even in patients with high HAS-BLED score.10 Calculation of net clinical benefit can be used to guide the use of OAC man-

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agreement by balancing the risk and benefit of treatment.\(^{10,11}\) However, data in Asian population is lacking and both patients and physicians are reluctant to prescribe OAC due to the belief that bleeding complications are related to the act of physicians.\(^{12}\)

We hypothesized that history of major bleeding may be associated with less use of OAC, and that this lower use of OAC may lead to poor clinical outcomes. The objectives of this study were to determine whether major adverse clinical outcomes (MACE) are related to a history of bleeding and choice of antithrombotic medications.

## 2 Methods

### 2.1 Study population

We conducted a prospective registry of patients with NVAF who were more than 18 years of age. Patients meeting any of the following criteria were excluded: (1) ischemic stroke within three months; (2) thrombocytopenia (< 100,000/mm\(^3\)), myeloproliferative disorders, hyperviscosity syndrome, or antiphospholipid syndrome; (3) prosthetic valve or valve repair; (4) rheumatic valve disease or significant valve disease; (5) atrial fibrillation from transient reversible cause (e.g., during respiratory tract infection or bronchospasm); (6) ongoing participation in a clinical trial; (7) life expectancy less than three years; (8) pregnancy; (9) inability to attend scheduled follow-up appointments; (10) refusal to join the study; and/or (11) current hospitalization or hospitalization within one month prior to inclusion in the study. This study was approved by the Institutional Review Boards of all participating hospitals. All patients gave written informed consent prior to participation. Study enrollment was during 2014 to 2017.

### 2.2 Data collection

The following data were collected: demographic data, types of NVAF, medical illness, components of CHA\(_2\)DS\(_2\)-VASc and HAS-BLED scores, history of bleeding and severity, investigations, and antithrombotic medications. All data were recorded on a case record form, after which the data was input into a web-based system for centralized data management. Random site monitoring was performed, and approximately 70% of sites were audited.

### 2.3 Outcome measurement

Clinical outcomes for this study were death, bleeding, and ischemic stroke/transient ischemic attack (TIA). All clinical events were adjudicated by the adjudication committee. Bleeding was classified as either major bleeding or minor bleeding. Major bleeding was defined as intracranial hemorrhage, intraspinal hemorrhage, intraarticular hemorrhage, intracocular/retinal hemorrhage, or intramuscular hemorrhage with compartment syndrome, or any bleeding that led to a reduction in hemoglobin of \(\geq 2\) mg/dL from baseline.\(^{13}\) Minor bleeding was defined as any bleeding that did not fulfill any of the criteria for major bleeding. For death event, the cause of death was collected and recorded.

### 2.4 Statistical analysis

We described continuous data by mean ± SD, and categorical data by number and percentage. Comparisons of continuous data between groups were made by Student’s \(t\)-test for unpaired data. For categorical data, comparisons were made by Pearson’s chi-square test or Fisher’s exact test. Univariate and multivariate analyses were performed to identify independent variables that predict clinical outcomes. The results of Cox proportional hazards regression analysis are given as hazard ratio (HR) with 95% confidence interval (CI). The log-rank test was used to compare the difference in the rate of clinical outcome between patients with and without a history of major bleeding. A \(P\)-value of less than 0.05 was considered statistically significant.

## 3 Results

A total of 3218 patients were included, the average age was 67.3 ± 11.3 years, and 58.3% were male. History of bleeding was recorded in 308 patients (9.6%). Sixty-nine patients (2.14%) had a history of major bleeding. Baseline characteristics of the study population and comparisons between patients with and without history of bleeding are shown in Table 1. Average CHA\(_2\)DS\(_2\)-VASc and HAS-BLED scores were 3.0 ± 1.7 and 1.5 ± 1.0, respectively. Patients with history of bleeding had older age, more diabetics, more ischemic stroke or TIA, and greater CHA\(_2\)DS\(_2\)-VASc and HAS-BLED scores compared to those without history of major bleeding.

Figure 1 demonstrates a comparison of patterns of antithrombotic use between patients with and without a history of major bleeding. There was no significant difference in the strategy of antithrombotic use between groups. Overall, 2126 patients (66.1%) received OAC alone, 555 (17.2%) received antiplatelet alone, 298 (9.3%) received both, and 239 (7.4%) received no antithrombotic drug. Among patients who received OAC, 220 (9.1%) used non-vitamin K antagonist anticoagulants (NOACs). Among 298 patients who were on OAC plus antiplatelet, only 50 patients (16.7%) had indication for OAC plus antiplatelet. OAC management was considered overtreated when OAC was prescribed in

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Table 1. Baseline characteristics of patients classified by history of major bleeding.

| Characteristic                  | All (n =3218) | With history of major bleeding (n = 69) | No history of major bleeding (n = 3149) | P-value |
|--------------------------------|--------------|----------------------------------------|----------------------------------------|---------|
| Age, yrs                       | 67.3 ± 11.3  | 70.8 ± 9.8                             | 67.2 ± 11.3                            | 0.010   |
| Male                           | 1875 (58.3%)| 46 (66.7%)                             | 1829 (58.1%)                           | 0.153   |
| BMI                            | 25.2 ± 4.8  | 24.2 ± 4.3                             | 25.2 ± 4.8                             | 0.104   |
| Hypertension                   | 2183 (67.8%)| 52 (75.4%)                             | 2131 (67.7%)                           | 0.176   |
| Diabetes                       | 778 (24.2%) | 26 (37.7%)                             | 752 (23.9%)                            | 0.008   |
| Dyslipidemia                   | 1803 (56.0%)| 40 (58.0%)                             | 1763 (56.0%)                           | 0.742   |
| Smoker                         | 650 (20.2%) | 20 (29.0%)                             | 630 (20.0%)                            | 0.066   |
| Heart failure                  | 878 (27.3%) | 17 (24.6%)                             | 861 (27.3%)                            | 0.618   |
| Implanted cardiac device      | 331 (10.3%) | 12 (17.4%)                             | 319 (10.1%)                            | 0.050   |
| Ischemic stroke or TIA         | 555 (17.2%) | 22 (31.9%)                             | 533 (16.9%)                            | 0.001   |
| CAD                            | 513 (15.9%) | 14 (20.3%)                             | 499 (15.8%)                            | 0.319   |
| CHA2DS2-VASc score             | 3.0 ± 1.7   | 3.6 ± 1.8                              | 3.0 ± 1.7                              | 0.004   |
| HAS-BLED score                 | 1.5 ± 1.0   | 2.7 ± 0.9                              | 1.5 ± 1.0                              | <0.001  |
| Cirrhosis                      | 36 (11%)    | 2 (2.9%)                               | 34 (1.1%)                              | 0.180   |
| CKD (available data = 2392)    | 1498 (62.6%)| 42 (72.4%)                             | 1456 (62.4%)                           | 0.119   |
| Renal replacement therapy      | 32 (1.0%)   | 2 (2.9%)                               | 30 (1.0%)                              | 0.149   |
| History of PCI or CABG         | 286 (8.9%)  | 9 (13.0%)                              | 277 (8.8%)                             | 0.220   |
| LVEF by echocardiogram         | 59.6 ± 14.7 | 64.2 ± 13.8                            | 59.5 ± 14.7                            | 0.013   |

Medications

| Drug                          | All (n =3218) | With history of major bleeding (n = 69) | No history of major bleeding (n = 3149) | P-value |
|-------------------------------|--------------|----------------------------------------|----------------------------------------|---------|
| Antiplatelet                  | 853 (26.5%)  | 18 (26.1%)                             | 835 (26.5%)                            | 0.936   |
| Anticoagulant                 | 2424 (75.3%) | 52 (75.4%)                             | 2372 (75.3%)                           | 0.994   |
| Warfarin                      | 2204 (68.5%) | 47 (68.1%)                             | 2157 (68.5%)                           | 0.946   |
| NOAC                          | 220 (6.8%)   | 5 (7.2%)                               | 215 (6.8%)                             | 0.809   |
| Beta blocker                  | 2345 (72.9%) | 50 (72.5%)                             | 2295 (72.9%)                           | 0.939   |
| Verapamil or diltiazem        | 109 (3.4%)   | 3 (4.3%)                               | 106 (3.4%)                             | 0.507   |
| Dihydropyridine CCBs          | 775 (24.1%)  | 17 (24.6%)                             | 758 (24.1%)                            | 0.913   |
| Digoxin                       | 510 (15.8%)  | 15 (21.7%)                             | 495 (15.7%)                            | 0.176   |
| Amiodarone                    | 288 (8.9%)   | 3 (4.3%)                               | 285 (9.1%)                             | 0.176   |
| Statin                        | 1887 (58.6%) | 41 (59.4%)                             | 1846 (58.6%)                           | 0.894   |
| Diuretic                      | 988 (30.7%)  | 23 (33.3%)                             | 965 (30.6%)                            | 0.632   |
| RAS blocker                   | 1565 (48.6%) | 35 (50.7%)                             | 1530 (48.6%)                           | 0.725   |
| NSAID                         | 78 (2.4%)    | 3 (4.3%)                               | 75 (2.4%)                              | 0.233   |
| Proton pump inhibitor         | 664 (20.6%)  | 23 (33.3%)                             | 641 (20.4%)                            | 0.008   |

Data are presented as means ± SD or n (%). BMI: body mass index; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CCBs: calcium channel blockers; CKD: chronic kidney disease (creatinine clearance < 60 mL/min); LVEF: left ventricular ejection fraction; NOAC: non-vitamin K antagonist oral anticoagulant; NSAID: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention; RAS: renin angiotensin system; TIA: transient ischemic attack.

patients with low risk of ischemic stroke, or OAC was combined to antiplatelet without indication, i.e., percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) within one year in intermediate or high risk patients. In our study, 356 patients (15.1%) out of 2350 were considered OAC overtreated (after excluding patients with PCI or ACS within one year and those who did not receive OAC). The duration of OAC plus antiplatelet treatment among 127 patients with history of PCI was 50.6 ± 43.8 months. For 102 patients with history of ACS, the duration of OAC plus antiplatelet treatment was 54.2 ± 54.1 months. Among 555 patients who were on antiplatelet alone, 54 (26.1%) had CHA2DS2-VASc of 0, 115 (20.7%) had coronary artery disease (CAD), 386 (69.5%) presumed to be on for NVAF. Among 239 patients who received no antithrombotic drug, 86 (36%) had CHA2DS2-VASc of 0, and 153 (64%) had no reasons for not being on OAC. Table 2 shows OAC and antiplatelet use compared between patients with and without history of major bleeding.
than six months, the follow-up duration was 22 ± 11 months, and the overall event rate that included death, ischemic stroke/TIA, and major bleeding was 9.9%. There were 124 episodes of major bleeding during follow-up. Sixty-nine episodes (55.6%) happened during taking OAC. Details for site of major bleeding from history and during follow-up are shown in Table 3. Among patients with remote history of upper gastro-intestinal bleeding, 44% received proton pump inhibitors. Among 25 patients with upper gastro-intestinal bleeding as the site of major bleeding from history, only one patient had upper gastro-intestinal bleeding as the site of major bleeding during follow-up. Table 4 shows the number of patients with each of these events compared between patients with and without history of major bleeding. Patients with history of major bleeding had a significantly higher overall rate of composite outcome (25.4%) compared with those without history of major bleeding (9.6%). Forest plot of univariate and multivariate analyses for predictors of the composite outcome is shown in Figure 2. Independent factors that predict composite outcomes were older age, hypertension, diabetes, heart failure, and history of major bleeding. Obesity was identified as a protective factor. Kap-lan-Meier survival analysis for composite events compared between patients with and without history of major bleeding is shown in Figure 3. Patients with history of major bleeding had a higher risk of death/ischemic stroke/TIA/major bleeding compared to those without a history of major bleeding, and the survival graph continues to separate until the end of the follow-up.

Figure 1. Types of antithrombotic drugs received by non-valvular atrial fibrillation patients. NOAC: non-vitamin K antagonist oral anticoagulants.
Table 4. Follow-up events (death, ischemic stroke/TIA, major bleeding) in patients with and without major bleeding.

| Type of events | All (n = 3115) | With history of major bleeding (n = 67) | No history of major bleeding (n = 3048) | P-value |
|----------------|----------------|----------------------------------------|---------------------------------------|---------|
| Death          | 183 (5.9%)     | 10 (14.9%)                              | 173 (5.7%)                            | 0.005   |
| Ischemic stroke/TIA | 78 (2.5%)     | 6 (9.0%)                                | 72 (2.4%)                             | 0.006   |
| Major bleeding | 124 (4.0%)     | 4 (6.0%)                                | 120 (3.9%)                            | 0.340   |
| Ischemic stroke/TIA or major bleeding | 189 (6.1%) | 10 (14.9%)                              | 179 (5.9%)                            | 0.006   |
| Death or Ischemic stroke/TIA or major bleeding | 309 (9.9%) | 17 (25.4%)                              | 292 (9.6%)                            | < 0.001 |

Data are presented as n (%). TIA: transient ischemic attack.

Figure 2. Univariate and multivariate analyses for factors predicting composite endpoint of death, ischemic stroke/TIA, and major bleeding. BMI: body mass index; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CI: confidence interval; CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio; LVEF: left ventricular ejection fraction; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; RRT: renal replacement therapy; TIA: transient ischemic attack.

Figure 3. Kaplan-Meier estimates of composite endpoint-free survival (death, ischemic stroke/TIA, and major bleeding) in non-valvular atrial fibrillation patients with and without history of major bleeding. TIA: transient ischemic attack.

Table 5 shows event rates according to antithrombotic treatment strategy in patients with and without history of major bleeding. Patients receiving no antithrombotic drugs, which is usually a low risk group, had a lower event rate compared to those with OAC alone, OAC plus antiplatelet, or antiplatelet alone. Patients receiving OAC plus antiplatelet had an increased risk of composite outcome compared to OAC alone. For ischemic stroke/TIA, patients with antiplatelet alone had a higher rate of ischemic stroke/TIA compared to those with OAC alone. Patients with OAC plus antiplatelet had a higher rate of major bleeding compared to antiplatelet alone and slightly higher than patients with OAC alone. We also performed a separate analysis for occurrence of event according to antithrombotic use in the groups with and without history of major bleeding. For patients with history of bleeding, although the sample size was relatively small (67 patients), we found that patients with OAC plus antiplatelet had a higher rate of death and also composite outcome compared to those with OAC alone or antiplatelet alone. Among patients with no history of major bleeding, the majority of patients not receiving antithrom-
Table 5.  Event rate according to the pattern of antithrombotic drugs in patients with and without history of major bleeding.

| Variable                              | All (n = 3115) | OAC alone (n = 2045) | OAC + APT (n = 293) | APT alone (n = 544) | None (n = 233) | P-value |
|---------------------------------------|----------------|----------------------|---------------------|---------------------|----------------|---------|
| All (n = 3115)                        |                |                      |                     |                     |                |         |
| Death                                 | 183 (5.9%)     | 112 (5.5%)           | 24 (8.2%)           | 39 (7.2%)           | 8 (3.4%)       | 0.055   |
| Ischemic stroke/TIA                   | 78 (2.5%)      | 43 (2.1%)            | 10 (3.4%)           | 22 (4.0%)           | 3 (1.3%)       | 0.029   |
| Major bleeding                        | 124 (4.0%)     | 89 (4.4%)            | 20 (6.8%)           | 14 (2.6%)           | 1 (0.4%)       | 0.001   |
| Composite outcome¹                    | 309 (9.9%)     | 195 (9.5%)           | 42 (14.3%)          | 60 (11.0%)          | 12 (5.2%)      | 0.004   |
| History of major bleeding (n = 67)    |                |                      |                     |                     |                |         |
| Death                                 | 10 (14.9%)     | 5 (11.1%)            | 4 (80.0%)           | 1 (7.7%)            | -              | 0.004   |
| Ischemic stroke/TIA                   | 6 (9.0%)       | 4 (8.9%)             | 1 (20.0%)           | 1 (7.7%)            | -              | 0.724   |
| Major bleeding                        | 4 (6.0%)       | 4 (8.9%)             | -                   | -                   | -              | 0.759   |
| Composite outcome¹                    | 17 (25.4%)     | 11 (24.4%)           | 4 (80.0%)           | 2 (15.4%)           | -              | 0.034   |
| No history of major bleeding (n = 3048)|                |                      |                     |                     |                |         |
| Death                                 | 173 (5.7%)     | 107 (5.4%)           | 20 (6.9%)           | 38 (7.2%)           | 8 (3.5%)       | 0.140   |
| Ischemic stroke/TIA                   | 72 (2.4%)      | 39 (2.0%)            | 9 (3.1%)            | 21 (4.0%)           | 3 (1.3%)       | 0.028   |
| Major bleeding                        | 120 (3.9%)     | 85 (4.3%)            | 20 (6.9%)           | 14 (2.6%)           | 1 (0.4%)       | 0.001   |
| Composite outcome¹                    | 292 (9.6%)     | 184 (9.2%)           | 38 (13.2%)          | 58 (19.0%)          | 12 (5.2%)      | 0.013   |

Data are presented as n (%). ¹Refer to death or ischemic stroke/TIA or major bleeding. APT: antiplatelet; OAC: oral anticoagulant; TIA: transient ischemic attack.

Antithrombotic drugs were in the low-risk group, and therefore had a lower rate of events compared to other groups. Patients receiving antiplatelet alone had a significantly higher rate of ischemic stroke compared to patients receiving OAC alone. Patients taking OAC plus antiplatelet had a higher rate of major bleeding compared to those taking OAC alone or antiplatelet alone. Patients receiving OAC plus antiplatelet had a higher rate of composite outcome compared to those taking OAC alone.

4 Discussion

We analyzed data from a multicenter atrial fibrillation registry to determine the effect of history of major bleeding on choices of antithrombotic treatment and clinical outcomes. From a multicenter registry of 3218 patients with NVAF in Thailand, 69 patients (2.14%) had history of major bleeding, and 2424 (75.3%) received OAC. There was no significant difference in pattern of antithrombotic use between patients with and without history of major bleeding but the therapeutic range (TTR) was lower in those with history of major bleeding. During the average follow-up of 22 months, death, ischemic stroke/TIA and major bleeding occurred in 5.9%, 2.5%, and 4.0%, respectively. Patients with history of major bleeding had a significantly higher rate of adverse clinical outcomes during follow-up. Patients with antiplatelet alone had a higher rate of ischemic stroke compared to those who received OAC. OAC plus antiplatelet increased risk of adverse outcome. Only 16.8% of patients with OAC plus antiplatelet were within one year after ACS or PCI. Inappropriate use of oral anticoagulant plus antiplatelet should be avoided.

Current practice guidelines for the management of patients with atrial fibrillation recommend the use of CHA₂DS₂-VASc and HAS-BLED score to assess the risk of ischemic stroke and bleeding, respectively.¹⁴,¹⁵ These guidelines emphasize that the assessment for bleeding risk should not be the reason for withholding the use of OAC, but to search for the factors that could be corrected to minimize the bleeding risk during the use of OAC. History of bleeding is a component of the HAS-BLED score, which was developed from the Euro Heart Survey database from 3963 patients with atrial fibrillation.⁹ In the Euro Heart Survey study, 61 patients had a history of major bleeding, which accounted for 1.5% of study population.⁹ Data from our study showed that 2.1% of our patients had a history of major bleeding, which is slightly higher than European data. One-year follow-up data from the Euro Heart Survey revealed a major bleeding rate of 1.5%.¹⁶ Our follow-up data for major bleeding event demonstrated a rate of 4.0% over an average follow-up duration of 22 months. This translates to a rate of 2.2% per year, which is also higher than the data from the Euro Heart Survey study. Data from the GARFIELD global atrial fibrillation registry showed that 2.9% of
The annual major bleeding event rate from two-year follow-up data from the GARFIELD registry was 0.7%, which is much lower than our data (2.2% per year).

There are some possible explanations for the higher proportion of history of bleeding and major bleeding, and also the rate of major bleeding during follow-up between our study and the Euro Heart Survey and the GARFIELD global registry. Firstly, data from recent NOAC trials indicated that Asian population had a significantly higher rate of major bleeding and intracerebral hemorrhage compared to Caucasians. Shen, et al. reported the rate of intracerebral hemorrhage during warfarin therapy to be four times in Asian population than in Caucasians from a study in a multi-ethnic cohort of 18,667 patients. Data from the FU-SHIMI-AF registry from Japan showed a history of major bleeding of 4.2%, which is greater than our study. Secondly, the rate of use of NOAC in our study was less than in the GARFIELD registry. The rate of NOAC use in GARFIELD study increased from 4.2% in Cohort 1 during 2010–2011 to 30% in Cohort 4 during 2014–2015. Our study was conducted during 2014–2017. We had a rate of NOAC use of only 6.8% of our entire study population, which is significantly less than the rate reported from the GARFIELD registry. Although recent guidelines give priority to NOAC compared to warfarin, it is our government policy to restrict the use of expensive drugs to reduce or contain the cost of treatment. This may result in a higher rate of major bleeding in our study population compared to the GARFIELD registry. More information may be needed in our population to convince the government that more money can be saved by preventing major events that occur due to the complications of NVAF than by restricting access to more expensive, but more effective medication options. When we compare our previous data from 2014–2015 with our 2016–2017 data, we can see that NOAC use is increasing even though the Thai government continues to restrict access to NOACs.

One-third of patients with major bleeding in the ORBIT-AF study discontinued OAC permanently. Those who discontinued OAC were more likely to have ischemic stroke compared to those who continued using OAC. It is important to emphasize that OAC should be restarted after treating the cause of major bleeding in order to minimize the risk of ischemic stroke in NVAF. In our study, pattern of antithrombotic use was not significantly different between patients with and without history of major bleeding. Data from the ARISTOTLE study showed that patients with history of bleeding had a significantly increased risk of future bleeding, but did not increase the risk of other events, such as ischemic stroke or death. However, the results from our study showed that patients with history of major bleeding increased risk of death, ischemic stroke, and composite outcome. Our data also showed that the risk for future major bleeding was doubled in patients with history of major bleeding compared to those without. The observed statistical non-significance may be due to the small number of events and small number of patients with history of major bleeding. The difference in the future risk of other events which is significant difference for the higher risk of death and ischemic stroke in our study but not in previous study may be related to several reasons. We used history of ‘major’ bleeding, but report from ARISTOTLE used history of bleeding which indicated a less severe subgroup. Secondly, OAC in our study is warfarin in the majority of patients, but previous report had a much higher rate of NOAC use. We also postulate that one of the reasons that patients with history of major bleeding had a higher rate of ischemic stroke may be related to a fear of bleeding from OAC among patients with history of major bleeding. Although the rate of OAC use is not different between patients with and without history of major bleeding, the time in TTR may be lower in patients with history of major bleeding due to a fear of bleeding. We performed additional analysis comparing TTR between patients with and without history of major bleeding. We found that the TTR to be lower in patients with history of major bleeding (44%) than in patients without history of major bleeding (51%), but the difference between groups was not statistically significant ($P = 0.139$).

Regarding event rate during follow-up, our data showed a similar rate of ischemic stroke compared to GARFIELD, Euro Heart Survey and FUSHIMI study, and a similar rate of death compared to GARFIELD data. The major bleeding rate was higher in our study than in the GARFIELD and Euro Heart Survey studies, but comparable to the FUSHIMI study. The rate of death in the FUSHIMI study was higher than the rate in our study; however, the mean age of the study population was higher in the FUSHIMI study than in our study. Comparisons of previous data on the history of major bleeding and clinical outcomes are demonstrated in Table 6.

We demonstrated that adding antiplatelet to OAC increased risk of major bleeding and possibly the risk of death. This finding confirms the results from previous study. Although practice guidelines for the management of patients with stable CAD and ACS emphasize that among patients with atrial fibrillation that need OAC, antiplatelet is not required in stable CAD or for at least one year after ACS or PCI, many physicians still use combination of OAC and antiplatelet without appropriate indications, which

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Table 6. Comparisons of results from previous studies and our study.

| Variable                        | European Heart Survey\[9\] | GARFIELD\[17\] | FUSHIMI\[19\] | Our study |
|---------------------------------|----------------------------|----------------|---------------|-----------|
| Year of publication             | 2010                       | 2016           | 2017          | NA        |
| Number of patients              | 3963                       | 17162          | 3878          | 3218      |
| History of major bleeding       | 1.5%                       | 2.9%           | 4.2%          | 2.1%      |
| Follow-up duration              | 1 year                     | 2 years        | 3 years       | 1.8 years |
| Major bleeding during follow-up/year | 1.5%              | 0.7%           | 1.6% female, 2.1% male | 2.2%      |
| Percentage of OAC               | 65%                        | 61%            | 54%           | 75%       |
| Percentage of NOAC (among OAC)  | 0%                         | 18%            | 18%           | 9%        |

OAC: oral anticoagulant; NA: not applicable; NOAC: non-vitamin K antagonist oral anticoagulants.

leads to increased risk among these patients. From our study, only 16.8% of patients with OAC plus antiplatelet were within one year after ACS or PCI. The results of our study also showed that adding antiplatelet to OAC not only increased the rate of major bleeding and death, but also increased the rate of ischemic stroke/TIA. We postulated that due to a fear of bleeding when combining OAC with antiplatelet, the TTR may be lower in patients with OAC plus antiplatelet compared to those without combination treatment. We performed additional analysis of TTR in patients receiving OAC compared between those taking and not taking antiplatelet. We found the TTR to be significantly lower in patients with OAC plus antiplatelet than in patients taking OAC alone (44% vs. 51%, P = 0.001). Therefore, inappropriate use of oral anticoagulant plus antiplatelet should be avoided. Our data showed that three main reasons for not using OAC in elderly population with NVAF were concomitant use of antiplatelet, patient refusal, and fear of bleeding.\[29\]

4.1 Limitations

This study has some limitations. Firstly, this registry enrolled patients mainly from tertiary care or university hospitals. This may limit the generalizability of our results. Secondly, the investigators in this registry are mainly cardiologists, which may explain the relatively high percentage of patients receiving OAC. Last but not least, we did not record data on anticoagulation circumstance during bleeding. However, for 124 episodes of major bleeding during follow-up, 69 episodes (55.6%) happened during taking OAC.

4.2 Conclusions

Sixty-nine patients (2.14%) had history of major bleeding. There was no significant difference in pattern of antithrombotic use compared between patients with and without history of major bleeding. Patients with history of major bleeding had a significantly higher rate of major adverse event during follow-up compared to those without history of major bleeding. Patients who received OAC plus antiplatelet had an increased risk of major adverse event.

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