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Letter to the Editors-in-Chief

Oral anticoagulant-associated bleeding requiring hospitalization in Thai patients: Incidences, risk factors, and outcomes

Oral anticoagulants have been widely used in patients with atrial fibrillation (AF), mechanical valve and in the treatment of both arterial and venous thromboembolism (VTE). Warfarin is the conventional oral anticoagulant which was established its efficacy and safety profiles. Direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban, and apixaban, have gained their popularity and been increasingly used since their approval in Thailand for stroke prevention in AF and VTE treatment.

Real world data from Asian countries suggests a lower incidence of bleeding in DOAC-treated Asian patients. A study using Korean National Health Insurances data showed that in AF, DOAC treatment was associated with a lower risk of intracranial hemorrhage compared with warfarin (1). A nationwide cohort study from Taiwan using National Health Insurance data demonstrated all DOACs were associated with a lower risk of major bleeding compared with warfarin among patients with AF (2). However, cohort analysis of the Japan medical data center claims databases in AF reported comparable incidences of total bleeding, gastrointestinal hemorrhage (GIH) and intracranial hemorrhage between DOACs and warfarin (3).

In Thailand, there is no available data regarding bleeding outcomes in patients on oral anticoagulants. Therefore, we conducted this study to provide a real-world experience on the incidences bleeding, bleeding characteristics, outcomes, and to identify risk factors associated with mortality.

1. Material and methods

A list of patients treated with oral anticoagulant including warfarin, dabigatran, rivaroxaban, or apixaban from January 2012 to December 2017 was retrieved from the hospital database. Patients who required hospitalization and had primary or secondary diagnoses of bleeding according to ICD 10 were identified. All patients were hospitalized because of bleeding. Bleeding events included: intracranial hemorrhage including intracerebral (ICH), subarachnoid (SAH), subdural (SDH), and epidural hemorrhages, GIH, and other bleedings. Electronic chart review was performed in all bleeding events to confirm the presence of anticoagulants. Baseline characteristics, type of anticoagulants, and the indication of treatment were recorded. In AF patients, risk factors for bleeding using HASBLED score (4), and risk factors for stroke using CHA_2DS_2VASc, score (5) were calculated. Need for surgical intervention, and mortality related with bleeding were recorded. Major bleeding was defined by the criteria according to the International Society on Thrombosis and Haemostasis (ISTH) definition (6). Descriptive statistics were used for baseline characteristics. The cumulative incidences of bleeding were calculated. Only first bleeding event was included in the analysis. The cumulative incidences of patients bled on warfarin were compared with those bled on DOACs using Chi-square test, and odds ratios (OR) were calculated. Risk factors for mortality associated with bleeding were identified using multiple logistic regression.

2. Results

A total of 9054 patients received warfarin, and 2599 received DOACs (631 patients received dabigatran, 1288 patients received rivaroxaban, and 680 patients received apixaban). The number of patients on DOACs increased significantly over the years from 86 in 2012 to 1549 in 2017. Median follow-up time were 2.62 years (Interquartile rage [IQR] 0.84–4.96) and 1.3 years (IQR 0.51–2.75) in warfarin- and DOAC- treated patients, respectively. Baseline characteristics of patients who bled are shown in Table 1. Overall cumulative incidence was 2.53%. Of the 260 first bleeding events, 240, 5, 5, and 10 occurred in warfarin-, dabigatran-, rivaroxaban-, and apixaban-treated patients, respectively. The cumulative incidences of bleeding requiring hospitalization were 2.65% and 0.76% (OR, 3.51, 95% confidence interval [CI], 2.2–6.86) in warfarin- and DOAC- treated patients, respectively. ICH, SDH, and GIH occurred in 0.56% and 0.15% (OR 3.67, 95% CI 1.34–14), 0.72% and 0.15% (OR 4.69, 95% CI 1.74–17), and 0.83% and 0.34% (OR 2.40, 95% CI 1.19–5.46) in warfarin- and DOAC- treated patients, respectively.

Of the 240 bleeding events with warfarin, major bleeding occurred in 203 (84.5%). The causes of bleeding were known in 193 patients (80.4%) The majority of bleeding events occurred spontaneously (162, 83.9%). Traumatic or post-procedural bleeding occurred in 31 (12.9%). SDH occurred more frequently than ICH (65, 31.7% and 51, 24.9%, respectively). The majority of patients with SDH were symptomatic (63, 97%). UGIH occurred more frequently than LGIH (43, 57.3% and 23, 30.7%, respectively) (Table 2). Other bleedings included retroperitoneal hemorrhage (8, 3.9%), intramuscular hematoma (9, 4.4%), mucocutaneous bleeding (13, 4.9%), post-procedural bleeding (4, 1.5%), and abnormal uterine bleeding (AUB) (4, 1.5%).

Of the 20 bleeding events with DOACs, major bleeding occurred in 13 (65%). The majority of bleeding events occurred spontaneously (16, 80%) whereas 4 (20%) were traumatic events. All dabigatran associated bleedings were GIH. UGIH occurred more frequently than LGIH (3, 60% and 1, 20%, respectively). Rivaroxaban associated bleedings were ICH in 2 (20%), SDH in 2 (20%). GIH occurred in 3 (30%) patients of which LGIH occurred in 2 (66.7%) of patients (Table 2). Other bleedings included one patient with AUB, one with hemarthrosis, and one with mucocutaneous bleeding. Apixaban associated bleeding was ICH in 2 (40%), SDH in 2 (40%) and UGIH in 1 (33%) patients. One of the SDH patients was symptomatic.

There were 34 deaths: 33 with warfarin and 1 with apixaban. Mortality rates were 13.8% and 5% in warfarin- and DOAC-associated bleeding, respectively. Fatal bleedings in warfarin were ICH in 14 (42.4%), SDH in 7 (21.2%), GIH in 8 (24.4%) and retroperitoneum in 4 (12%) patients. One fatal bleeding with apixaban was an ICH.

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Table 1
Baseline characteristics of patients with bleeding requiring hospitalization.

Baseline characteristics	Warfarin (n = 240)	Dabigatran (n = 5)	Rivaroxaban (n = 10)	Apixaban (n = 5)
Age, median (IQR)	72 (61.5–79)	82 (82–82)	70.5 (60–80)	77 (72–81)
Male, n (%)	117 (48.8)	1 (20)	8 (80)	3 (60)
Indication, n (%)				
- Atrial fibrillation	150 (62.5)	4 (80)	7 (70)	5 (100)
- VTE	22 (9.17)	1 (20)	3 (30)	
- Others	42 (17.5)			
Hypertension, n (%)	139 (57.9)	4 (80)	4 (40)	3 (60)
Diabetes, n (%)	75 (31.3)	0	0	3 (60)
Previous stroke, n (%)	71 (29.6)	1 (20)	3 (30)	5 (100)
Previous CHF, n (%)	17 (7.1)	1 (20)	1 (10)	0
Vascular disease, n (%)	48 (20)	1 (20)	1 (10)	0
Previous major bleeding, n (%)	9 (3.8)	0	2 (20)	1 (20)
Renal disease, n (%)	62 (25.8)	2 (40)	1 (10)	1 (20)
Liver disease, n (%)	10 (4.2)	0	0	0
Concomitant use of antiplatelet or NSAIDS, n (%)				
- Aspirin	35 (14.6)	0	3 (30)	0
- Clopidrogrel	7 (2.9)	0	0	1 (20)
- Aspirin + Clopidogrel	4 (1.7)	0	0	0
- Celecoxib	1 (0.4)	0	0	0
CHADSVASC score, median (IQR)[a]	3 (3–5)	5 (3.5–6)	3 (3–4)	5 (4–7)
HASBLED score, median (IQR)	2 (1–3.5)	3 (2–3)	2 (1–3)	4 (3–4)
TTR (median, IQR)	33.6 (6.4–56.1)	–	–	–
Labile INR	83.1%	–	–	–
Median follow-up (years, IQR)	1.45 (0.3–4.1)	1.2 (0.4–2.9)	0.36 (0.02–1.2)	0.43 (0.04–1.4)

SD = standard deviation, IQR = interquartile range, VTE = venous thromboembolism, APS = antiphospholipid antibody syndrome, CHF = congestive heart failure, LA = left atrial, NSAID = non-steroidal anti-inflammatory drug, TTR = time in therapeutic range.
[a] Calculated only patients with atrial fibrillation.

Table 2
Location of all bleeding events by type of oral anticoagulants[a]

Location of bleeding (n, %)	Warfarin (n = 240)	Dabigatran (n = 5)	Rivaroxaban (n = 10)	Apixaban (n = 5)
ICH	51 (21.3)	–	2 (20)	2 (40%)
SDH	65 (27.1)	–	2 (20)	2 (40%)
SAH	12 (5)	–	1 (10)	–
EDH	6 (2.5)			
UGIH	43 (18)	3 (60)	–	1 (20)
LGIH	23 (9.6)	1 (20)	2 (20)	–
Undetermined GIH	9 (3.8)	1 (20)	1 (10)	–
Retroperitoneal hemorrhage	8 (3.3)	–	–	–
Others	37 (1.54)	–	3 (30)	–

ICH = intracerebral hemorrhage, SDH = subdural hemorrhage, SAH = subarachnoid hemorrhage, EDH = epidural hemorrhage, GIH = gastrointestinal hemorrhage, UGIH = upper gastrointestinal hemorrhage, LGIH = lower gastrointestinal hemorrhage.
[a] Some patients had more than one bleeding sites.

The case-fatality rate of intracranial hemorrhage including ICH, SDH, and SAH, was 17.6% with warfarin and 12.5% with DOACs. Among patients with intracranial hemorrhage, surgical intervention was required in 47 (39.5%) with warfarin but none with DOACs. The case-fatality rate of GIH was 10.7% with warfarin. The case-fatality rate of retroperitoneal bleeding associated with warfarin was 50%.

By univariate analysis, ICH, history of vascular disease, renal disease, embolization were associated with mortality. By multivariate analysis, ICH, renal disease and embolization were significantly associated with mortality. Adjusting for age, sex, and type of anticoagulant, ICH (OR 4.3, 95% CI 1.96–9.51), renal disease (OR 2.42, 95% CI 1.05–5.55) and requirement for embolization (OR 6.9, 95% CI 1.44–33) were associated with an increased risk for mortality.

3. Discussion

During a 6-year-period, the cumulative incidence of overall bleeding associated with oral anticoagulant was 2.53% in this study. The incidences of bleeding requiring hospitalization, ICH, and GIH associated with warfarin were significantly higher than those associated with DOACs. Patients bled on DOACs had a lower fatality rate and required a lower number of surgical intervention for intracranial bleeding. Our results support the lower incidence of bleeding with DOACs previously reported in other Asians.

Overall, patients bled on DOACs had higher baseline bleeding risks i.e. higher median age, more frequent history of previous major bleeding, higher HASBLED compared to those bled on warfarin. Nonetheless, patients on DOACs have a lower overall incidence of bleeding and mortality. This could be implied that DOACs are better-tolerated and might be preferable options in patients with high bleeding risk.

With warfarin, intracranial bleeding occurred slightly more often than GIH. Consistent with the previous literature, SDH was the most common intracranial bleeding (7). With rivaroxaban and apixaban, there was no preferential site of bleeding between intracranial and gastrointestinal tracts, whereas, dabigatran bled more in the gastrointestinal tract.

Patients bled on warfarin had higher mortality than those who bled on DOACs. Mortality with warfarin occurred in patients with intracranial, gastrointestinal, and retroperitoneal hemorrhages. The latest had the highest case-fatality rate. One fatal event occurred with apixaban use in a patient with AF. This patient had previous intracranial hemorrhage and recent embolic stroke. Since only one death occurred with DOAC, case-fatality rate could be overestimated.

For intracranial hemorrhage, surgical interventions were required in nearly half of patients with warfarin whereas no surgical intervention was required in patients with DOACs. The case-fatality rate for intracranial hemorrhage with DOACs was also lower than warfarin. This provides additional evidence that intracranial hemorrhage associated with DOACs use has lower mortality compared with warfarin despite no specific antidote use (8).

We found that ICH, renal impairment, and the need for embolization were associated with mortality. High fatality rate would be

expected with intracerebral hemorrhage (9). Patients required embolization were likely to have inadequate bleeding controlled by medication and not suitable for surgery. Renal impairment, especially end-stage renal disease on hemodialysis, was associated with high mortality (10,11).

The strength of our study is that to our knowledge this is the first real-world data in Thailand that demonstrate the incidences of bleeding associated with warfarin and DOACs. We included the use of oral anticoagulant for all indications. All bleeding events and the presence of oral anticoagulants were reviewed and confirmed.

The study also has limitations. Baseline characteristics of patients who did not bleed were not feasible to obtain. Thus we could not adjust the risk factors of bleeding. Due to the retrospective design, there were a number of missing data. The risk factors for mortality in our study would not be applicable to DOACs associated bleeding since there was only one fatality in DOAC treated-patients. Most of the fatal events occurred in warfarin treated-patients. The data in our study were collected over a period of 6 years therefore the bleeding management may have changed over the years. Although we did not have an independent committee to adjudicate the outcomes, all bleeding episodes were reviewed by the authors from medical records.

In conclusion, the incidences of bleeding requiring hospitalization found among Thai patients receiving oral anticoagulants were low. Patients receiving warfarin had higher cumulative incidences of bleeding requiring hospitalization, intracerebral hemorrhage, and gastrointestinal hemorrhage than those receiving DOACs. Intracerebral hemorrhage, renal impairment, and the requirement for embolization were associated with an increased risk for mortality.

Authors' contributions

Contribution: K.B., P.A. designed the project. K.B. reviewed, analyzed, interpreted data and wrote the manuscript. P.A. critically revised the manuscript. P.K. retrieved hospital data. All authors have read and approved the submitted manuscript.

Declaration of competing interest

No competing financial interests.

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