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Research Article

Assessment of direct-acting oral anticoagulants for the treatment of venous thromboembolism in cancer patients in Thai Tertiary Care Hospital

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ABSTRACT

Venous thromboembolism (VTE) is an important cancer complication. Recent studies suggest direct-acting oral anticoagulants (DOACs) are possible alternatives for this population; nonetheless, there is limited evidence to support this decision in Thai cancer patients. The primary aim of this study was to measure the cumulative incidence of VTE recurrences and major bleeding among cancer patients who received DOACs that were available in Thailand. Secondary objective was to determine factors associated recurrent VTE and major bleeding. This is a retrospective cohort study conducted in tertiary care hospitals in Thailand. Data was collected from patients who had active cancer with new diagnosis of VTE and receiving approved DOACs. There were 32 cases, who received rivaroxaban, apixaban, or dabigatran, recruited to this study. We reported 4 cases (12.5%) of recurrent VTE at 6-month. There were 6 patients (18.75%), 2 patients (6.25%), and 1 patient (3.13%) with major bleeding, minor bleeding and intracranial hemorrhage, consecutively. No correlation was found between factors associated with recurrent VTE recurrence or bleeding. This study demonstrated that DOACs may be an acceptable option for preventing VTE recurrence. However, Thai population may be potentially prone to have clinically relevant bleeding. A further prospective study is warranted to draw a final conclusion in Thai cancer patients

Keywords:
Direct-acting oral anticoagulant, Cancer-associated thrombosis, VTE, Venous thromboembolism, Malignancy

1. INTRODUCTION

Venous thromboembolism (VTE) is a common complication in cancer patients and is considered to be a major risk of death compared to patients without cancer. Several studies have shown that the cancer associated with VTE has a three- to eight-fold mortality rate[1-2]. Furthermore, cancer treatment, including but not limited to certain types of anticancer and targeted therapy, is prompted by a thrombosis risk. The location of the primary tumor has been established as an independent risk factor for VTE in several studies. Specific incidence rates vary based on the clinical setting. However, pancreatic, stomach, uterine, and lung carcinomas are among the types of cancer that have been described as higher VTE incidences[3-7]. Besides, certain chemotherapeutic agents have been considered as an additional risk factor, such as thalidomide, or anti-vascular endothelial growth factors (VEGF)[8]. Moreover, there is a trivial amount of evidence of increased VTE risk in patients receiving Platinum-based chemotherapy. Additionally, treatments for cancer patients are unfortunately complicated by bleeding at higher rates than for those without cancer[9-10].

Current guidelines acquiesce to therapy options for cancer-associated thrombosis which include low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, and fondaparinux and direct-acting oral anticoagulants.These include the American College of Chest Physician (ACCP), the National Comprehensive

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Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO)[11-13]. Interestingly, there are growing evidences regarding the efficacy and safety of DOACs in this population both in clinical trials and meta-analyses[14-23]. DOACs are currently approved for VTE and/or stroke prevention that available in Thailand are rivaroxaban, dabigatran, apixaban, and edoxaban. Rivaroxaban, apixaban, and edoxaban are direct inhibitors of factor Xa, while dabigatran acts as a direct thrombin inhibitor. In contrast to warfarin, the DOACs do not require routine therapeutic drug monitoring, are not concerned with dietary restrictions, and are expected to have less extensive drug-drug or drug-food interactions, making these medications attractive. However, some limitations are still warranted in DOACs users specifically in chronic kidney diseases as these are mainly excreted through kidneys[22]. DOACs have been integrated into the treatment recommendations in all of the published guidelines in cancer associated thrombosis (CAT). In general, DOACs are recommended for patients at low risk for bleeding who do not have gastrointestinal (GI) or genitourinary (GU) malignancies, who have adequate renal (and hepatic function, according to the NCCN guidelines), and who do not have any significant drug-drug interactions in their medical history. Patients with gastrointestinal or genital malignancies or who have had substantial drug-drug interactions should be prescribed LMWH[12-13]. Nonetheless, there is limited information to support this decision in Thai cancer patients.

The purpose of this study was to determine the cumulative rates of recurrent VTE and bleeding in cancer patients receiving a DOAC based on real-world evidence. We also looked into the relationship between various risk factors for VTE or bleeding, whenever possible, in order to improve awareness of anticoagulant monitoring in this patient population.

2. MATERIALS AND METHODS

This is a retrospective cohort study that was approved by the Institutional Review Board (IRB) committee. It was conducted in academic medical centers. The study enrolled patients with an active cancer diagnosis who were receiving Thai FDA-approved DOACs (dabigatran, apixaban, edoxaban, or rivaroxaban) for the treatment of VTE between November 2013 and November 2017. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision Thai Modification (ICD-10-TM) codes were used to identify the data. The primary outcome measure was the cumulative rate of recurrent VTE in cancer patients receiving DOACs six months after starting the DOACs. Secondary outcomes included the recurrence of VTE and bleeding in patients treated with each DOAC in the study. Patients were followed for 12 months after the initial thrombotic event, and all outcomes were assessed at any point following the initial diagnosis. The demographic characteristics of the patients were presented as a percentage, mean, and standard deviation (SD). Fischer's exact test was used to compare categorical variables, and Student's unpaired t-test was used to compare continuous variables when necessary. The statistic was validated using a 0.05 two-sided alpha value. SPSS version 18 was used to conduct all data analyses (SPSS Inc., Chicago, Illinois, USA).

3. RESULTS

3.1. Baseline Characteristic

Fifty-one percent of the 32 patients included in our final report were female. These patients had an Eastern Cooperative Oncology Group (ECOG) score ranging from 0 to 2. Rivaroxaban was the most frequently prescribed agent (16/32 cases) in our study. The majority (59.4 percent) of VTE cases occur in patients with stage III disease. The most frequently reported type of VTE was DVT in the proximal lower limb, which occurred in 50% of cases. Six patients (18.7 percent) had a prior history of anticoagulant use. Two patients were on warfarin, three were on anticoagulants for atrial fibrillation, and one had gastrointestinal bleeding. Ovarian cancer (9 cases; 27.3 percent) and lung cancer (5 cases; 15.2 percent) were the most frequently reported active cancers. At the time of the index VTE, nearly all of the patients (29/32 cases) were receiving chemotherapy. For cancer treatment, the majority of patients (43.8 percent and 40.6 percent, respectively) received chemotherapy using platinum complexes and/or taxane derivatives. Our study revealed comorbidities such as hypertension (22 cases; 34.9 percent), diabetes (14 cases; 22.2%), and cardiovascular diseases (14 cases; 22.2 percent. Additionally, 25% of patients received antiplatelets or non-steroidal anti-inflammatory drugs (NSAIDs) concurrently with DOAC initiation. The baseline characteristics of our patients are summarized in Table 1.

3.2. Recurrent VTE and bleeding outcomes

Cumulative VTE recurrence in DOAC-treated individuals was 12.5% at six months (4 patients). There were no new cases of VTE at the end of the year. Rethrombosis occurred after a median time of 5.4 months. Three out of four patients, according to the Khorona criteria, were categorized as "very high risk" or "high risk" for developing VTE. Among patients with recurrent VTE, two out of four cases were discovered in patients who had previously completed warfarin for provoke VTE. Following that, all patients with recurrent DVT were given LMWH. Table 2 summarizes the patient characteristics of each recurrent DVT case. There was no statistically significant difference between DOAC types

Table 1. Patients Baseline Characteristic.

Characteristics	n (%)
Gender	
Female	16 (51.6)
Age (Years±SD)	59.6±11.3
ECOG performance status (%)	
0	25 (78.1)
1	6 (18.8)
2	1 (3)
Cancer staging	
2	7 (21.9)
3	19 (59.4)
4	6 (18.7)
Type of cancers	
Ovarian	9 (27.3)
Lung	5 (15.2)
Stomach	3 (9.1)
Pancreas	2 (6.1)
Breast	5 (15.2)
Chemotherapy	
Platinum-based compound	14 (43.8)
Venous thromboembolism location	
Pulmonary Embolism	4 (12.5)
Proximal lower limb	16 (50.0)
Concurrent medications	
Antiplatelet or NSAIDs	8 (25.0)
Colony stimulating factor	9 (28.0)
Erythropoietin	6 (18.8)
Type of Direct oral anticoagulants	
Rivaroxaban	16 (50.0)
Dabigatran	8 (25.0)
Apixaban	8 (25.0)
History previous anticoagulants	6 (18.8)
Platelet count (10^3 per uL±SD)	179±22
Serum creatinine (mg/dL±SD)	0.79±0.09
International normalized ratio (INR±SD)	0.46±0.09

ECOG-eastern cooperative oncology group
NSAIDs-non-steroidal anti-inflammatory drugs

Table 2. Patients with recurrent venous thromboembolism.

Case	Gender	Age (years)	Cancer type	Staging	DOACs type	Management after recurrences
1	Female	55	Ovarian	2	Dabigatran	Enoxaparin
2	Male	73	Stomach	3	Apixaban	Enoxaparin
3	Male	44	Brain	3	Apixaban	Enoxaparin
4	Female	44	Ovarian	2	Dabigatran	Enoxaparin

DOACs-direct-acting oral anticoagulants

in patients with recurrent DVT (Figure 1)

According to the International Society on Thrombosis and Haemostasis (ISTH) criteria, major bleeding is defined as bleeding associated with at least one of the following: transfusion of at least two units of packed red blood cells, a decrease in hemoglobin of more than two grams per deciliter, and bleeding in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, or intramuscular). The combined (major and non-major) bleeding rate at 6 months was 25%, with major bleeding accounting for 18.8 percent. The median time to bleeding was three months. Each case of clinically relevant bleeding is described in Table 3. The gastrointestinal tract, intracranial, genitourinary, and subcutaneous tissues were the site of bleeding in our report. Bleeding occurs in patients with lung, ovary, lymphoma, and bladder cancer. There were three cases of clinically significant bleeding in which antiplatelet or non-steroidal anti-inflammatory therapy was used concurrently. Furthermore, there was no statistically significant difference in bleeding occurrence between DOAC types, as shown in Figure 1.

Additionally, we examined the association between predefined risk factors and recurrent VTE or clinically significant bleeding. The findings indicate that no correlation exists between those risks and clinical outcomes in both thrombosis and hemorrhage events. In the context of recurrent VTE, risk factors included a history of previous anticoagulant use (RR 4.33; 95 percent confidence interval [CI] 0.75-27.87; *P*=0.1000),

Table 3. Patients with bleeding complications.

Gender	Age (years)	Cancer type	Staging	DOACs	Major bleeding	Site of bleed	Management after bleeding
Male	67	Lung	3	Rivaroxaban	No	Bleeding gum	DOACs continued
Male	47	Non-Hodgins Lymphoma	3	Rivaroxaban	Yes	Gastrointestinal bleeding	Hold DOACs and resumed
Female	53	Ovarian	2	Rivaroxaban	No	Bruising	DOACs continued
Male	53	Bladder	3	Dabigatran	Yes	Hematuria	DOACs discontinued
Female	65	Lung	4	Rivaroxaban	Yes	Gastrointestinal bleeding	DOACs discontinued
Female	64	Ovarian	3	Rivaroxaban	Yes	Spontaneous hematoma	DOACs discontinued
Male	57	Lung	3	Dabigatran	Yes	Gastrointestinal bleeding	DOACs discontinued
Male	71	Brain	3	Rivaroxaban	Yes	Intracranial Bleeding	DOACs discontinued

DOACs-direct-acting oral anticoagulants

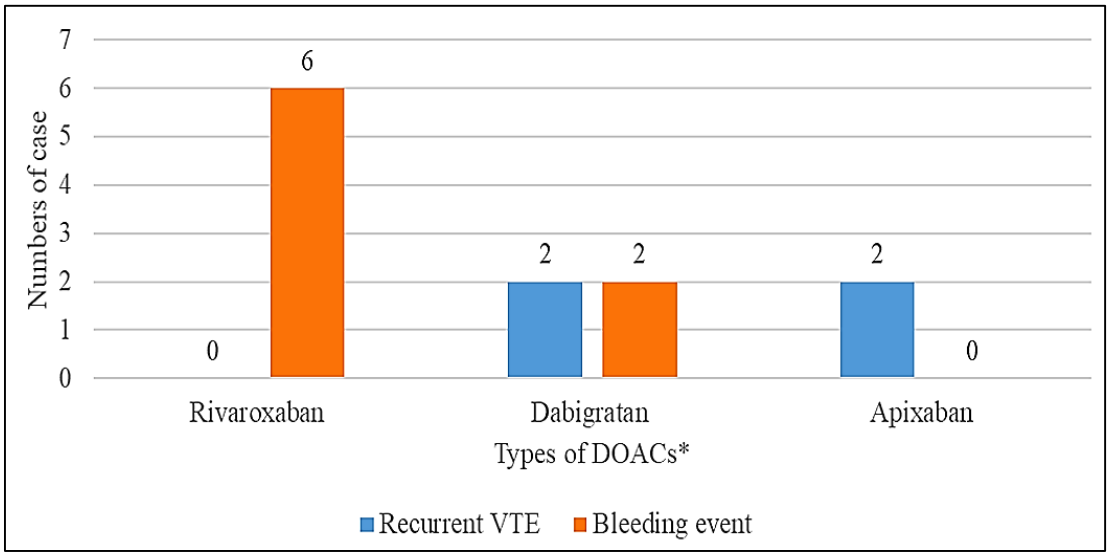

Figure 1. Number of case with reported recurrent VTE and bleeding outcomes by type of DOACs
* = DOACs = direct-acting oral anticoagulants

very high or high risk cancer types (RR 1.57; 95 percent CI 0.18-13.39; *P*=0.6792), and use of platinum-based chemotherapy (RR 3.86; 95 percent CI 0.45-33.20; *P*=0.219). Similarly, the RR of concurrent antiplatelet or NSAID use was 1.80 (95% CI 0.55-5.89; *P*=0.3317), whereas the RR of metastasis status was 0.87 (95% CI 0.12-6.12; *P*=0.8859).

4. DISCUSSION

Historically, subcutaneous LMWH has been the treatment of choice for secondary prophylaxis of VTE recurrence in cancer patients. There were studies including the meta-analysis compared the efficacy of LMWH to warfarin and discovered that LMWH had a significantly lower recurrence rate of VTE at six months[22-24]. DOACs and their approval for the treatment of VTE expand treatment options that are likely to be more tolerable, convenient for patients, and ostensibly more adherent. Although direct-acting oral anticoagulants (DOACs) are preferred for the treatment of VTE in patients without cancer, their role in cancer patients remains debatable specifically in some population[15-17]. Several recent studies have shown that DOACs may have an equivalent or lower incidence of recurrent VTEs compared to dalteparin, but they also have linked with a higher risk of bleeding. A previous meta-analysis, which included results from the Hokusai VTE Cancer, the SELECT-D, and the ADAM VTE trials, found that DOACs were associated with a nonstatistically significant relative risk reduction in VTE recurrence in cancer patients compared to patients treated with LMWH in cancer patients. DOACs, on the other hand, were shown to be connected with a higher risk of significant bleeding and clinical relevant non-major bleeding (CRNMB), among other things. Most current recommendations

continue to advocate dalteparin as the first line of defense against VTEs in cancer patients, with DOAC therapy advised solely as an alternative[16]. More-over, in another meta-analysis, DOACs were shown to be non-inferior to dalteparin in terms of reducing the risk of VTE recurrence in patients. When dalteparin was used DOACs, the risk of recurrent VTE was 1.55 times higher. More importantly, despite the fact that DOACs were linked with a higher risk of CRNMB as compared to dalteparin, the risk of major bleeding was comparable between the two treatment groups and not statistically significant difference[18].

According to our retrospective findings, the majority of cases of VTE recurrence occur within the first six months following a confirmed VTE and the initiation of anticoagulation. The majority of VTE cases in our study occurred in patients with stage III cancer, which is consistent with established data demonstrating a strong association between advanced cancers and the incidence of VTE. Similarly, hemorrhagic events of clinical significance occur early in the course of treatment, regardless of the anticoagulant used. Our findings indicated slightly higher bleeding rates when compared to recent prospective data from the HOKUSAI-VTE Cancer study and the Select-D, both of which compared the use of dalteparin with edoxaban (HOKUSAI-VTE) or rivaroxaban (Select-D) in patients with cancer who had an acute VTE. As with our report, all patients enrolled in the SELECT-D trial and approximately 95% in the Hokusai VTE Cancer trial had active cancer at the time of enrollment[17,19]. However, in light of recurrent VTE, the majority of our patients were diagnosed as having active cancer with a very high risk of recurrence or a high-risk type of cancer based on the Khorona classification and a history of anticoagulation, which may have contributed to the higher recurrence rate. Our overall bleeding event rate was also higher than that reported in recent studies, at 25%. However, owing to the small number of cases, determining causation may be challenging. Numerous explanations may be proposed, including but not limited to the fact that individuals undergoing chemotherapy are also at risk of bleeding due to thrombocytopenia, the cancer's stage, or drug-drug interaction[25]. Our study's major bleeding sites were similar to those reported previously, namely the gastrointestinal tract, genitourinary system, central nervous system, and skin and soft tissue. The gastrointestinal tract was the most frequently bled area. This finding is consistent with two previous DOACs in cancer trials, which demonstrated an increased risk of gastrointestinal bleeding in patients receiving a DOAC versus conventional therapy, specifically in GI malignancy[17-19]. In contrast, our patients who experienced severe bleeding were from a diverse range of cancer diagnoses, which included patients with primary brain tumors as well as patients with brain metastases or hematologic malignancy, who were typically excluded from the various trials because they were thought to be at high risk of severe bleeding. The greater risk of bleeding seen in our research might possibly be contributed by this factor. All major bleeding events in our study necessitated the discontinuation of DOACs, and the majority were discontinued permanently regardless of the cause of the hemorrhages. However, due to the limitations of our medical record system, it was difficult to determine whether fatal bleeding was caused solely by anticoagulation.

The study's strengths include the inclusion of real-world practice in the management of VTE across the spectrum in Thai cancer patients, pre-specified and independent analysis of the study's most interesting outcomes, and the use of a uniform definition of bleeding. Nonetheless, several potential limitations of this retrospective study should be recognized. It is possible that there were cases of VTE recurrence or clinically significant VTE at other facilities during the 12-month follow-up period, or that there were no records in medical records. This may result in an erroneous decrease in the rate of complications. There is reason to believe that, given the retrospective nature of this study, selection bias in our cohort may have been confounded. Additionally, we reported on a small number of patients who used DOACs, which may lack the statistical power necessary to detect statistically significant and noteworthy potential risks. This is because our internal hospital consensus on cancer-related VTE is consistent with other guidelines, and our drug of choice at the moment remains LMWH, specifically enoxaparin. More importantly, the study's design incorporates numerous confounding variables that may interact with the desired outcomes. Additionally, this study was conducted in a small number of medical facilities, which may not be representative of all Thai cancer patients. However, with these concerns in mind, our current study offers essential information on the clinical out-comes of cancer associated thrombosis (CAT) which will be relevant for institutions where CAT is encountered in routine clinical practice.

5. CONCLUSIONS

Anticoagulation in cancer patients with VTE presents distinct concerns, including a higher risk of bleeding and recurrence of VTE than in non-cancer patients. Some clinical trial data suggest that DOACs are not inferior to LMWH in terms of preventing recurrent VTE. DOACs may be considered in Thai cancer patients who have limitations in the treatment of VTE due to LMWHs or warfarin to prevent recurrent VTE. It may be linked to an increased risk of clinically significant VTE and bleeding. DOACs should be used with caution in Thailand. To reach a final conclusion about Thai cancer patients, more prospective research is needed.

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Conflict of interests
The authors declare that they have no conflict of interest.

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Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Faculty of Dentistry/ Faculty of Pharmacy, Mahidol University, Institutional Review Board MU-DT/PY-IRB 2017/065.3010).

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