J Gynecol Oncol. 2022 Sep;33(5):e62
https://doi.org/10.3802/jgo.2022.33.e62
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Efficacy of edoxaban for the treatment of gynecological cancer-associated venous thromboembolism: analysis of Japanese real-world data

Suguru Odajima [1], **Toshiyuki Seki** [1], **Sayako Kato** [2], **Keisuke Tomita** [3], **Yuichi Shoburu** [1], **Eitaro Suzuki** [4], **Masataka Takenaka** [1], **Motoaki Saito** [3], **Hirokuni Takano** [4], **Kyosuke Yamada** [2], **Aikou Okamoto** [1]

[1]Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan
[2]Department of Obstetrics and Gynecology, Daisan Hospital, The Jikei University School of Medicine, Tokyo, Japan
[3]Department of Obstetrics and Gynecology, Kashiwa Hospital, The Jikei University School of Medicine, Chiba, Japan
[4]Department of Obstetrics and Gynecology, Katsushika Medical Center, The Jikei University School of Medicine, Tokyo, Japan

Received: Jan 11, 2022
Revised: May 11, 2022
Accepted: May 23, 2022
Published online: Jun 7, 2022

Correspondence to
Toshiyuki Seki
Department of Obstetrics and Gynecology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-0003, Japan.
Email: t_seki@jikei.ac.jp

ORCID iDs
Suguru Odajima
https://orcid.org/0000-0003-1000-1974
Toshiyuki Seki
https://orcid.org/0000-0002-7559-7089
Sayako Kato
https://orcid.org/0000-0001-5188-5783
Keisuke Tomita
https://orcid.org/0000-0002-1661-8097
Yuichi Shoburu
https://orcid.org/0000-0001-6533-3234
Eitaro Suzuki
https://orcid.org/0000-0002-9684-8860

ABSTRACT

Objective: Direct oral anticoagulants (DOACs) are increasingly being used for the treatment of cancer-associated venous thromboembolism (CAT). However, there is limited evidence of the efficacy of DOACs for the treatment of gynecological CAT. Thus, this study aimed to investigate the efficacy and safety of edoxaban for the treatment of gynecological CAT using Japanese real-world data.
Methods: We reviewed the medical records of patients with 371 gynecological cancer who received edoxaban or vitamin K antagonist (VKA) between January 2011 and December 2018.
Results: Altogether, 211 and 160 patients were treated with edoxaban and VKA, respectively. Fourteen patients (6.8%) in the edoxaban group and 22 (13.8%) in the VKA group showed recurrence of venous thromboembolism (VTE). Cumulative VTE recurrence was not significantly different between the 2 groups (p=0.340). Adverse events occurred in 15 (7.1%) and 11 (6.9%) patients in the edoxaban and VKA groups, respectively (p=0.697). Subgroup analysis of the edoxaban and VKA groups according to different tumor types, including ovarian, endometrial, and cervical cancer, showed equivalent outcomes in terms of VTE recurrence and adverse events. Patients without pulmonary embolism (PE) were mostly omitted from initial unfractionated heparin (UFH) therapy prior to administration of edoxaban. However, this did not increase the recurrence of VTE.
Conclusion: This study confirmed that edoxaban is effective and safe for the treatment of gynecological CAT. This finding was consistent for different types of gynecological cancer. Additionally, initial UFH therapy prior to the administration of edoxaban may be unnecessary for patients without PE.

Keywords: Gynecologic Neoplasm; Venous Thromboembolism; Anticoagulant Drugs

Masataka Takenaka
https://orcid.org/0000-0002-3833-4730
Motoaki Saito
https://orcid.org/0000-0001-6764-8459
Hirokuni Takano
https://orcid.org/0000-0002-6465-7883
Kyosuke Yamada
https://orcid.org/0000-0002-5216-7297
Aikou Okamoto
https://orcid.org/0000-0002-5079-0464

Presentation
The 72nd Annual Congress of the Japan Society of Obstetrics and Gynecology, Tokyo, April 2020.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: O.S., O.A.; Data curation: O.S., K.S., T.K., S.Y., S.E.; Investigation: O.S.; Writing - original draft: O.S., S.T.; Writing - review & editing: S.T., K.S., T.K., S.Y., S.E., T.M., S.M., T.H., Y.K., O.A.

Synopsis
Evidence of the efficacy of direct oral anticoagulants for the treatment of gynecological cancer-associated thrombosis (CAT) remains limited. This study demonstrated that edoxaban is effective and safe for the treatment of gynecological CAT. This result was consistent for different tumors, such as ovarian, endometrial, and cervical cancers.

INTRODUCTION

Patients with cancer have a 4-to-7-fold increased risk for venous thromboembolism (VTE) compared with people without cancer [1,2]. Management of cancer-associated venous thromboembolism (CAT) is extremely important because it can cause death and interrupt cancer treatment [3,4]. Vitamin K antagonists (VKAs) and low-molecular-weight heparin (LMWH) are generally used to treat CAT [5]. However, direct oral anticoagulants (DOACs) were recently approved for the treatment of CAT based on the results of clinical trials that showed the non-inferiority of DOACs to LMWH in terms of efficacy and safety [6-8]. Therefore, the current guidelines for the management of CAT recommend the use of DOACs, as well as LMWH, for the management of CAT. Consequently, DOACs are being increasingly used for the treatment of CAT [9-11].

Regarding gynecological malignancies, it was reported that 25%–38% of patients with gynecological cancers have VTE; therefore, they are regarded as high-risk patients. In accordance with the aforementioned pan-cancer guidelines, the Society of Gynecological Oncology Clinical Statement strongly recommends that patients with gynecological CAT should receive long-term treatment (at least 3–6 months) using LMWH or DOACs [12]. However, this recommendation is based on the results of trials conducted primarily on mixed populations with different types of cancer and a small number of patients with gynecological cancer. Indeed, only 10.5% of the study population of the Hokusai VTE Cancer study, which showed the noninferiority of edoxaban to dalteparin, were patients with gynecological cancer [6]. Considering that there is relatively little evidence of the efficacy of DOACs for the treatment of gynecological malignancies, we reckon that it is important to verify the efficacy and safety of DOACs for the treatment of gynecological cancers using Japanese real-world data. Therefore, this retrospective study was conducted to investigate the efficacy and safety of edoxaban (Lixana®; Daiichi Sankyo, Tokyo, Japan), which is the first DOAC approved in Japan and the most utilized for the treatment of gynecological CAT compared with VKA.

MATERIALS AND METHODS

This study was approved by the Jikei University ethical review board of the institutes participating in this study (31-018 [9517]). Informed consent was obtained from the participants by providing an opt-out option on participating institutional websites. We reviewed the medical records of 371 patients with gynecological malignancies, including ovarian, uterine, and cervical cancers, who received edoxaban or VKA treatment for VTE at the participating 4 hospitals between January 2011 and December 2018. All patients had symptomatic or non-symptomatic pulmonary embolism (PE) and/or deep vein thrombosis (DVT). Patients with borderline ovarian malignancy or synchronous cancer were excluded. Patients were also excluded if they had a history of thrombosis.

After the diagnosis of cancer, the D-dimer (D-d) levels of all patients were routinely measured for CAT screening. The patients were subsequently followed-up by physicians depending on their symptoms and the occurrence of events, including tumor recurrence and surgery, during cancer management. If a patient's D-d level exceeded 1.0 μg/mL regardless of symptoms and/or if a patient showed any symptoms related to CAT, such as pain, swelling, leg tenderness, unexplained shortness of breath, or chest pain, contrast-enhanced computed tomography (CT) and/or lower limb ultrasonography were performed for the diagnosis of VTE. After the diagnosis of VTE, follow-up examinations, which included contrast-enhanced CT or ultrasonography, were performed periodically.

The anticoagulant drug administered to each patient was selected by a physician. Edoxaban was approved by the Pharmaceutical and Medical Devices Agency of Japan in September 2014, whereas LMWH has not yet been approved; thus, VKA was the only option in Japan until September 2014. Each physician decided whether unfractionated heparin (UFH) should be administered as an initial anticoagulant prior to VKA or edoxaban. The UFH dose was adjusted to ensure that the patient's activated partial thromboplastin time (APTT) was in the therapeutic range of 40–60 seconds. The dose of edoxaban was 30 mg/day for patients who weighed less than 60 kg and 60 mg/day for those who weighed more than 60 kg. Patients with renal dysfunction whose creatinine clearance was between 30 and 50 mL per minute were administered 30 mg/day of edoxaban. The initial VKA dose was determined by each physician and adjusted toward a target prothrombin time-international normalized ratio of 2.0 (range, 1.5–2.5).

The primary efficacy outcome was VTE recurrence, defined as new symptomatic or asymptomatic PE or DVT. The primary safety outcome was the occurrence of any clinically relevant adverse event. In accordance with the criteria provided by the International Society on Thrombosis and Haemostasis, major bleeding was defined as overt bleeding associated with a decrease in hemoglobin level of 2 g per deciliter or more, leading to transfusion of 2 or more units of blood [13]. Clinically relevant non-major bleeding was defined as any overt bleeding events during the therapeutic period that did not meet the criteria for major bleeding but resulted in medical attention, unappointed visits, discontinuation of anticoagulants, or a decrease in patients' activities.

Patients' characteristics, including age, body weight, tumor type, International Federation of Gynecology and Obstetrics (FIGO) stage of tumor, histological diagnosis, symptoms, VTE site, timing of VTE diagnosis during the oncological clinical course, D-d value at the first diagnosis of VTE, VTE recurrence, all adverse events, induction of UFH therapy, duration of UFH therapy, and entire duration of anticoagulant therapy, were retrieved. Follow-up duration was calculated as the duration from the date of VTE diagnosis to the date of the last follow-up.

Statistical analyses were performed using EZR software version 1.37 (Saitama Medical Center, Jichii Medical University, Saitama, Japan) [14]. Continuous variables were compared using unpaired t-tests. Categorical variables are presented as absolute numbers and/or percentages and were compared using the χ^2 test. To compare the occurrence of adverse events between the 2 treatment groups, the time to VTE recurrence was analyzed using a Cox proportional-hazards model. Time-to-event curves were calculated using the Kaplan-Meier method. The significance level was set at $p<0.05$.

https://doi.org/10.3802/jgo.2022.33.e62

RESULTS

1. Patient characteristics

We identified a total of 371 patients with gynecological CAT treated with edoxaban or VKA between January 2011 and December 2018. The background data of all patients are summarized in **Table 1**. In total, 211 (56.9%) and 160 (43.1%) patients were treated with edoxaban and VKA, respectively. The follow-up duration was 19.0±16.1 and 38.7±28.0 months in the edoxaban and VKA groups, respectively. This difference in follow-up duration is attributable to timing of the approval of edoxaban. The use of edoxaban was officially approved in 2014 and has been increasingly utilized since then (**Fig. S1**). Of the 371 patients included in this study, 212 (57%) had ovarian cancer, which was the most common type of cancer, 98 (26%) had endometrial cancer, and 61 (17%) had cervical cancer. The patients treated with edoxaban were older than those treated with VKA (edoxaban, 62.2±11.4 vs. VKA, 60.0±11.7, p=0.051). There were no differences in clinical stage, histological type, VTE site, and timing of VTE diagnosis during the oncological course between the edoxaban and VKA groups. More patients in the VKA group underwent initial UFH therapy than in the edoxaban group. Patient background data according to cancer type are also described in **Table 1**. For ovarian and endometrial cancer, the proportion of patients with stage III/IV cancer was higher than the proportion of those with stage I/II cancer. For cervical cancer, the proportion of patients with stage I/II cancer was higher than the proportion of those with stage III/IV cancer (not significant). Moreover, most patients with ovarian and endometrial cancer were diagnosed with VTE before the initial treatment of cancer, whereas patients with cervical cancer were mostly diagnosed at the time of cancer recurrence.

In addition, 31% of the patients in the edoxaban group did not receive initial UFH therapy, as recommended by the Food and Drug Administration (FDA) [15].

2. Recurrence of VTE and adverse events

In this study, 14 (6.8%) patients in the edoxaban group and 22 (13.8%) in the VKA group showed recurrence of VTE (**Table 2**). There was no difference in the cumulative VTE recurrence between the edoxaban and VKA groups (hazard ratio, 0.714; 95% confidence interval, 0.356–1.432; p=0.340) (**Fig. 1**). Regarding the relationship between VTE recurrence and tumor status, more than half of VTE recurrence events occurred simultaneously with cancer recurrence in both treatment groups (**Table 2**). For the subgroup analysis, we analyzed cumulative VTE recurrence in patients with different types of cancer, including ovarian, endometrial, and cervical cancers. There was no significant difference in the cumulative risk of VTE recurrence between the edoxaban and VKA groups for each type of cancer (**Fig. 1**).

Regarding safety outcomes, adverse events were observed in 15 (7.1%) cases in the edoxaban group and 11 (6.9%) in the VKA group (p=0.697) (**Table 3**). Of these, 15 (7.1%) cases in the edoxaban group and 7 (4.4%) in the VKA group required discontinuation of anticoagulants. Bleeding events were among the most frequent adverse events in both treatment groups. Six cases of major bleeding events were recorded in the edoxaban group, and 3 cases were recorded in the VKA group (**Table 3**). Details of the major bleeding events are described in **Table S1**. There were 4 cases of gastrointestinal bleeding and 2 cases of intraperitoneal bleeding in the edoxaban group. Of note, the 2 cases of intraperitoneal bleeding were noted in patients with ovarian cancer who had intraperitoneal bleeding due to peritoneal carcinomatosis, which is one of the typical conditions of ovarian cancer, distinct from other types of solid cancer. One case of intraperitoneal bleeding and 2 cases of urogenital hemorrhage were recorded in the VKA group (**Table S1**).

https://doi.org/10.3802/jgo.2022.33.e62

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Table 1. Patients' background

Characteristics	Total (n=371)			Ovarian cancer (n=212)			Endometrial cancer (n=98)			Cervical cancer (n=61)		
	Edoxaban	VKA	p-value	Edoxaban	VKA	p-value	Edoxaban	VKA	p-value	Edoxaban	VKA	p-value
Cases	211	160		124	88		52	46		35	26	
Age	62.4±11.4	60.0±11.7	0.051	62.0±11.1	60.6±11.6	0.375	65.4±9.8	61.0±11.5	0.046	59.3±14.1	56.2±12.3	0.373
Body weight (kg)	53.4±10.2	54.4±11.1	0.386	52.3±9.9	51.5±8.8	0.559	55.7±10.6	59.7±12.6	0.094	54.1±10.1	54.9±11.9	0.766
≤60	152 (72)	119 (74)	0.695	95 (77)	71 (81)	0.590	34 (66)	28 (61)	0.679	23 (66)	20 (77)	0.506
>60	59 (28)	41 (26)		29 (23)	17 (19)		18 (34)	18 (39)		12 (34)	6 (23)	
Stage			0.702			0.733			0.681			1.000
I/II	90 (43)	69 (43)		46 (37)	37 (42)		24 (46)	18 (39)		20 (57)	14 (54)	
III/IV	120 (57)	89 (56)		77 (62)	50 (57)		28 (54)	27 (59)		15 (43)	12 (46)	
Unknown	1 (0)	2 (1)		1 (1)	1 (1)		0 (0)	1 (2)		0 (0)	0 (0)	
Histology			0.173			0.691			0.273			0.254
Adeno	172 (82)	125 (78)		115 (93)	84 (95)		45 (87)	36 (78)		12 (34)	5 (19)	
Non-adeno	36 (17)	35 (22)		7 (5)	4 (5)		6 (12)	10 (22)		23 (66)	21 (81)	
Unknown	3 (1)	0 (0)		2 (2)	0 (0)		1 (1)	0 (0)		0 (0)	0 (0)	
Site of VTE			0.372			0.573			0.544			0.015
PE±DVT	94 (45)	63 (39)		55 (44)	35 (40)		23 (44)	24 (52)		16 (46)	4 (15)	
DVT only	117 (55)	97 (61)		69 (56)	53 (60)		29 (56)	22 (48)		19 (54)	22 (85)	
Symptom			0.235			0.039			1.000			0.438
Present	58 (28)	54 (34)		23 (18)	28 (32)		19 (37)	17 (37)		16 (46)	9 (35)	
Absent	153 (72)	106 (66)		101 (82)	60 (68)		33 (63)	29 (63)		19 (54)	17 (65)	
Timing of diagnosis of VTE			0.108			0.524			0.283			0.204
At tumor diagnosis*	109 (52)	89 (56)		76 (61)	60 (68)		25 (48)	22 (48)		8 (22)	7 (27)	
Postoperative period†	19 (9)	26 (16)		9 (7)	9 (10)		7 (13)	12 (26)		3 (9)	5 (19)	
During chemotherapy‡	33 (16)	17 (11)		22 (18)	12 (14)		4 (8)	4 (9)		7 (20)	1 (4)	
Tumor recurrence§	39 (19)	21 (13)		12 (10)	4 (5)		13 (25)	8 (17)		14 (40)	9 (31)	
Observational period‖	11 (5)	7 (5)		5 (4)	3 (3)		3 (6)	0 (0)		3 (9)	4 (19)	
D-d at first diagnosis PE/DVT (μg/mL)	11.0±11.6	12.5±14.2	0.277	11.6±10.6	14.3±15.2	0.137	10.5±15.3	11.1±10.8	0.832	9.4±7.6	8.7±15.2	0.810
Induction of UFH												
(+)	66 (31)	131 (82)	<0.001	40 (32)	75 (85)	<0.001	16 (31)	40 (87)	<0.001	10 (29)	16 (62)	0.018
(−)	145 (69)	29 (18)		84 (68)	13 (15)		36 (69)	6 (23)		25 (71)	10 (38)	
Period of UFH (days)	10.2±9.0	16.6±13.1	<0.001	11.9±10.4	18.2±12.2	0.007	6.1±3.9	15.3±15.9	0.023	10.2±7.2	12.7±6.9	0.387
Period of oral anticoagulant (days)	388.8±370.2	462.6±558.7	0.131	401.3±364.6	460.5±515.3	0.332	455.6±422.4	468.7±620.1	0.903	245.1±263.6	459.0±611.2	0.071
≤3 mo	47 (22)	33 (21)	0.910	27 (22)	12 (14)	0.184	6 (12)	14 (30)	0.103	14 (40)	7 (27)	0.517
3–6 mo	38 (18)	29 (18)		21 (17)	19 (22)		11 (21)	5 (11)		6 (17)	5 (19)	
6–12 mo	40 (19)	35 (22)		20 (16)	22 (25)		14 (27)	10 (22)		6 (17)	3 (12)	
≥12 mo	86 (41)	63 (39)		56 (45)	35 (39)		21 (40)	17 (37)		9 (26)	11 (42)	

Values are presented as number (%) or mean ± standard deviation.
adeno, adenocarcinoma; D-d, D-dimer; DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
*Tumor diagnosis was defined before the first oncology treatment.
†The postoperative period was defined as the first 30 days after surgery.
‡During the period of postoperative adjuvant chemotherapy or initial chemotherapy.
§VTE occurred with tumor recurrence simultaneously.
‖The observational period was defined as the post-tumor treatment period without tumor burden.

https://ejgo.org https://doi.org/10.3802/jgo.2022.33.e62

Table 2. Recurrence of VTE

Characteristics	Total		Ovarian cancer		Endometrial cancer		Cervical cancer	
	Edoxaban (n=211)	VKA (n=160)	Edoxaban (n=124)	VKA (n=88)	Edoxaban (n=52)	VKA (n=46)	Edoxaban (n=35)	VKA (n=26)
VTE recurrence	14 (6.6)	22 (13.8)	10 (8.0)	7 (8.0)	4 (7.7)	9 (19.6)	0 (0)	6 (23)
Use of anticoagulant at VTE recurrence								
On anticoagulant	8	8	5	2	3	2	0	4
Off anticoagulant	6	14	5	5	1	7	0	2
Timing of VTE recurrence								
Postoperative period*	1	5	0	2	1	2	0	1
During chemotherapy†	1	3	1	1	0	2	0	0
Tumor recurrence‡	9	14	7	4	2	5	0	5
Observational period§	3	0	2	0	1	0	0	0

Values are presented as number (%) unless otherwise specified.
VKA, vitamin K antagonist; VTE, venous thromboembolism.
*Postoperative period was defined as the first 30 days after surgery.
†During the period of postoperative adjuvant chemotherapy or initial chemotherapy.
‡VTE occurred with tumor recurrence simultaneously.
§Observational period was defined as the post-tumor treatment period without tumor burden.

3. Comparison of the outcome between patients underwent initial UFH or not (single-drug) in the edoxaban group

It is recommended that UFH therapy should be administered with edoxaban at the beginning of VTE treatment [6,15]. However, 66 out of 211 (31%) patients in the edoxaban group did not undergo initial UFH therapy (single-drug subgroup) (**Tables 1** and **4**). Therefore, we decided to investigate the initial administration of UFH therapy before edoxaban further.

Assessment of the history of UFH use showed that initial UFH therapy was omitted over time during the study period (**Fig. S2**). The proportion of patients with PE was significantly higher in the UFH subgroup than in the single-drug subgroup (65% in the UFH subgroup and 35% in the single-drug subgroup, p<0.001) (**Table 4**). All patients who underwent initial UFH therapy required in-hospital management at the beginning of anticoagulant therapy, whereas only 46% of patients in the single-drug subgroup started anticoagulant therapy in hospital. Five (8%) and 9 (6%) patients in the UFH and single-drug subgroups, respectively, showed VTE recurrence (p=0.943) (**Table 4**). Cumulative VTE recurrence was not significantly different between the UFH and single-drug subgroups (p=0.882) (**Fig. 2**).

We also investigated the short-term outcomes of VTE recurrence, which is the initial 30 days after VTE recurrence. No case of VTE recurrence was recorded in the UFH subgroup within that period. However, one case of VTE recurrence was recorded in the single-drug subgroup (p=1.000). Moreover, no adverse event was recorded in either subgroup within the initial 30 days of anticoagulant therapy.

DISCUSSION

In this retrospective study, we demonstrated that edoxaban is effective and safe for the treatment of gynecological CAT using a large amount of patient data. To our knowledge, this is the first study to show the efficacy of edoxaban for the treatment of ovarian, endometrial, and cervical CAT through subgroup analysis of different tumor types. Additionally, this study showed that initiation of UFH therapy may not be necessary for patients without PE.

Based on the results of a series of clinical trials, including the Hokusai VTE Cancer (edoxaban vs. dalteparin, n=522 vs. 524), Caravaggio (apixaban vs. dalteparin, n=576 vs. 579), and

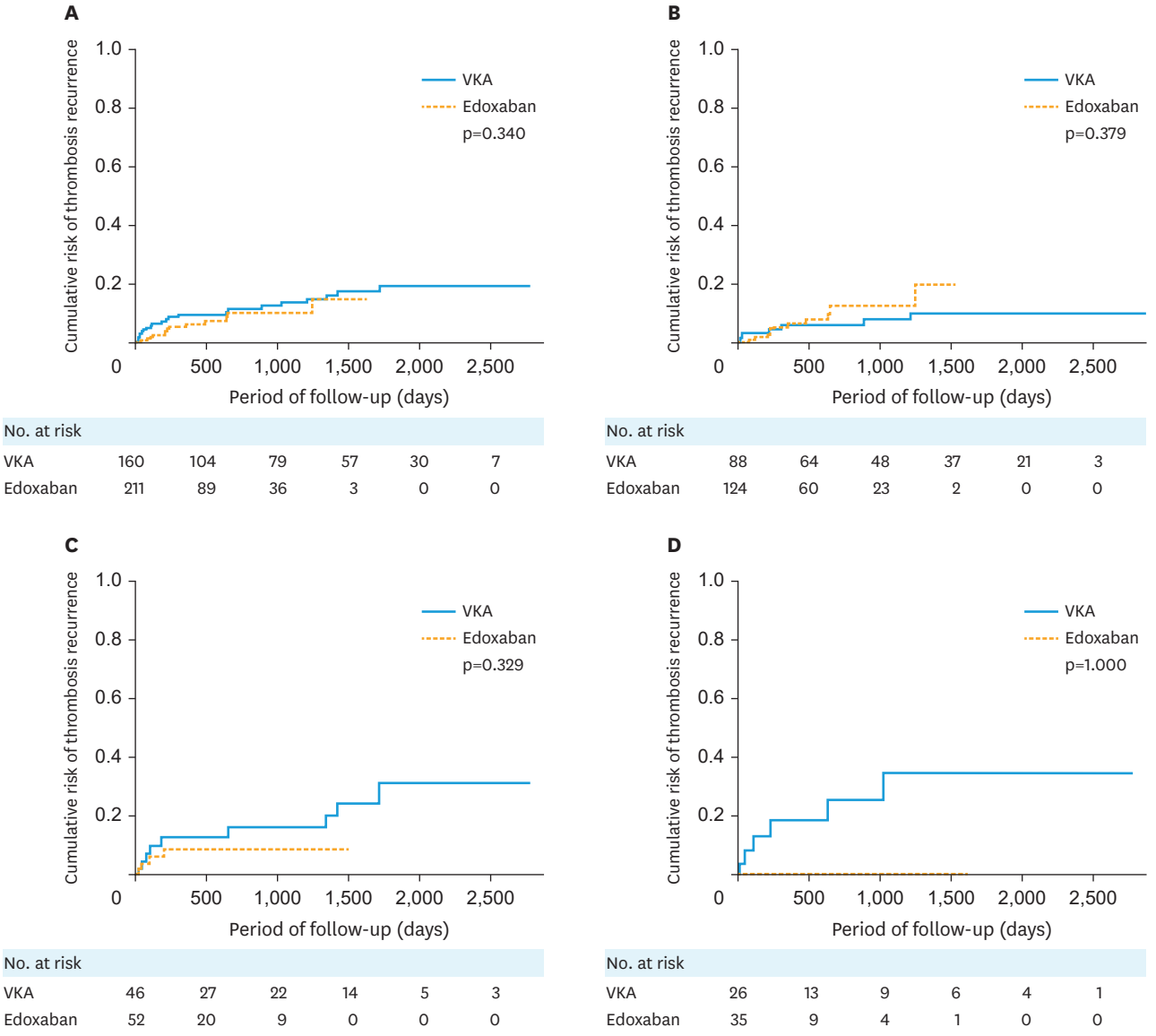

Fig. 1. Cumulative recurrence of VTE in the VKA and edoxaban groups. (A) All cancer types; (B) Ovarian cancer; (C) Endometrial cancer; (D) Cervical cancer. Kaplan-Meier cumulative event rates for the recurrence of venous thromboembolism. There was no significant difference between the time to VTE recurrence for all patients and patients with each cancer type in the VKA and edoxaban groups.
VKA, vitamin K antagonist; VTE, venous thromboembolism.

SELECT-D (rivaroxaban *vs.* dalteparin, n=203 vs. 203) trials, and meta-analyses including these trials, DOACs are considered effective, safe, and useful for the treatment of CAT [6-8]. These trials showed that the rate of VTE recurrence in patients treated with DOACs ranges from 4% to 8% and that of major bleeding events ranges from 3% to 7%, which is not inferior to the rates for LMWH [16]. Indeed, some guidelines recommend using DOACs, as well as LMWH, for the treatment of CAT. The guidelines provided by the American Society of Clinical Oncology recommend edoxaban and rivaroxaban for the treatment of CAT, whereas those by the National Comprehensive Cancer Network recommend edoxaban, apixaban, and rivaroxaban [12]. Unfortunately, patients with gynecological cancer were a relatively minor cohort in the abovementioned trials. There were 110 (10.5%) cases of gynecological cancer in the Hokusai VTE Cancer trial, which included 1,050 cases in total, 119 (10.3%)

https://doi.org/10.3802/jgo.2022.33.e62

Table 3. Adverse events

Characteristics	Total		p-value	Ovarian cancer		Endometrial cancer		Cervical cancer	
	Edoxaban (n=211)	VKA (n=160)		Edoxaban (n=124)	VKA (n=88)	Edoxaban (n=52)	VKA (n=46)	Edoxaban (n=35)	VKA (n=26)
Adverse event			0.697						
(+)	15 (7.1)	11 (6.9)		10 (8.1)	6 (6.8)	1 (1.9)	2 (4.3)	4 (11.4)	3 (11.5)
(–)	196 (92.9)	149 (93.1)		114 (91.9)	82 (93.2)	51 (98.1)	44 (95.7)	31 (88.6)	23 (88.5)
Discontinuation due to adverse event	15 (7.1)	7 (4.4)		10 (8.1)	4 (4.5)	1 (1.9)	1 (2.2)	4 (11.4)	3 (11.5)
All bleeding events	11 (5.2)	7 (4.4)		7 (5.6)	4 (4.5)	1 (1.9)	1 (2.2)	3 (8.6)	2 (7.7)
Major bleeding	6	3		3	0	1	1	2	2
CRNM bleeding	5	4		4	4	0	0	1	0
Poor control of PT-INR or APTT	0	7		0	2	0	2	0	3
Liver damage	3	0		3	0	0	0	0	0
Allergy	1	0		0	0	0	0	1	0

Values are presented as number (%) unless otherwise specified. Major bleeding was defined as a decrease of 2 g/dL or more in hemoglobin levels or a requirement for transfusion of 2 or more units of red cell concentrate. CRNM bleeding was defined as any overt bleeding events during the therapeutic period that did not meet the criteria for major bleeding but resulted in medical attention, unappointed visits, discontinuation of anticoagulants, or a decrease in daily activities.
APTT, activated partial thromboplastin time; CRNM, clinically relevant non-major; PT-INR, prothrombin time-international normalized ratio; VKA, vitamin K antagonist.

Table 4. Comparison of patients in the UFH and single-drug subgroups in the edoxaban group

Characteristics	UFH (n=66)	Single-drug (n=145)	p-value
Site of VTE			<0.001
PE±DVT	43 (65)	51 (35)	
DVT only	23 (35)	94 (65)	
Location of anticoagulant induction			<0.001
In hospital	66 (100)	66 (46)	
Outpatient	0 (0)	79 (54)	
VTE recurrence			0.943
(+)	5 (8)	9 (6)	
(–)	61 (92)	136 (94)	
VTE recurrence within the initial 30 days of anticoagulation			1.000
(+)	0 (0)	1 (1)	
(–)	66 (100)	144 (99)	
Adverse events within initial 30 days of anticoagulation			1.000
(+)	0 (0)	0 (0)	
(–)	66 (100)	145 (100)	

Values are presented as number (%) unless otherwise specified.
DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

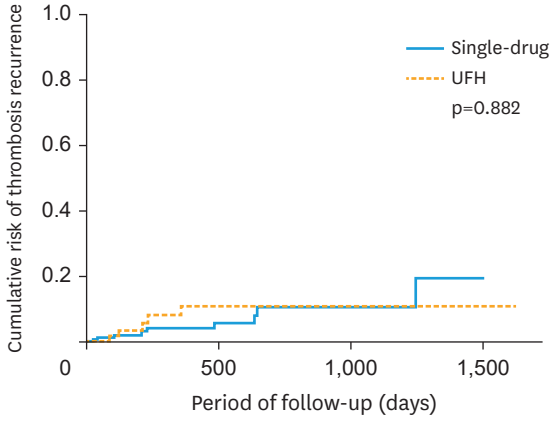

Fig. 2. Cumulative recurrence of VTE in patients with initial UFH and single-drug subgroups in the edoxaban group. Kaplan-Meier cumulative event rates for the recurrence of venous thromboembolism. There was no significant difference between the time to VTE recurrence in the unfractionated heparin and single-drug groups.
UFH, unfractionated heparin; VTE, venous thromboembolism.

https://doi.org/10.3802/jgo.2022.33.e62

in the Caravaggio trial, which included 1,155 cases in total, and 13 (3.2%) in the SELECT-D trial, which included 406 cases. Notably, subgroup analysis of different cancer types was performed in the Hokusai VTE Cancer trial [17]. In that trial, the outcomes of patients with gynecological cancer were analyzed, and the results showed that edoxaban is just as effective and safe as dalteparin. The authors reported that 3 (6.3%) patients treated with edoxaban and 9 (14.3%) treated with dalteparin experienced VTE recurrence, whereas 2 (4.2%) patients treated with edoxaban and 2 (3.2%) treated with dalteparin had on-treatment major bleeding. Unfortunately, subgroup analysis for gynecological malignancies was not performed in the other 2 trials.

Regarding other data on the use of DOACs for the treatment of gynecological CAT, Lee et al. [18] conducted a retrospective analysis of data on the use of rivaroxaban for the treatment of gynecological CAT. A total of 102 and 60 cases were included in the rivaroxaban and dalteparin groups, respectively, making it the largest study on the use of DOACs for gynecological CAT until the present study was performed. In that study, 6 (5.9%) patients treated with rivaroxaban and 4 (6.7%) treated with dalteparin experienced recurrent VTE, whereas major bleeding occurred in 8 (7.8%) and 3 (5.0%) patients treated with rivaroxaban and dalteparin, respectively. Likewise, Shimizu et al. [19] also performed a retrospective study that compared the outcome of DOACs and VKA for gynecological CAT. In the study, 54 and 53 patients were included in the DOACs and VKA groups, respectively, and 3 of the 53 patients (5.7%) in the VKA group developed recurrent VTE; there was no VTE recurrent patient in DOACs group, and only 1 patient (1.9%) in the DOACs group showed clinically relevant bleeding. In this study, 14 (6.6%) and 11 (5.2%) of the 211 patients who received edoxaban and 22 (13.8%) and 11 (6.9%) of the 160 patients who received VKA for the treatment of CAT experienced VTE recurrence and major bleeding, respectively. Cumulative recurrence of VTE was also equivalent between edoxaban and VKA. Accordingly, the outcome of edoxaban and VKA for gynecological CAT is equivalent in terms of efficacy and safety. Therefore, this study, which was performed on a larger scale than any previous prospective and retrospective studies, provides evidence that supports the existing data on the efficacy of DOACs for the treatment of gynecological CAT.

Previously reported data on the efficacy of DOACs for the treatment of gynecological CAT do not include analysis according to tumor types within gynecological malignancies, probably because of the small number of cases included in previous studies. In the Hokusai VTE Cancer trial, only 19, 15, and 10 cases of ovarian, endometrial, and cervical cancer, respectively, were included in the edoxaban group, whereas 33, 22, and 4 cases were included in the dalteparin group. It is important to consider that different cancers are associated with different degrees of risks for VTE because of factors such as patient's characteristics, histological type of the tumor, tumor stage, and treatment regimen [20-24]. The risk for VTE recurrence is also affected by tumor features [25]. A previous study showed that the VTE risk was approximately 14-fold higher in patients with gynecologic cancer than without cancer, indicating DVT and PE incidence, ranging from 17% to 40% and 1% to 2.6%, respectively [26-28]. In detail, ovarian cancer, especially the clear cell carcinoma type, is reported to be associated with a higher risk for VTE than other types of gynecological malignancies. The patients have adenocarcinoma, a high rate of advanced disease, and are at high-risk of tumor recurrence, thereby requiring highly invasive surgery and chemotherapy [23,29-31]. We could see some difference in response to anticoagulants between tumors in our results. The curve of cumulative VTE of the edoxaban group runs higher than VKA in ovarian cancer, whereas VKA run higher than edoxaban, and these differences may reflect tumor-specific features.

In addition, the risk of bleeding during anticoagulant therapy is influenced by the tumor site of origin, tumor stage, chemotherapy agents, radiation therapy, and surgery [32,33]. In this context, we believe that the data of each type of gynecological malignancy would be useful in deciding on the anticoagulant to be administered. To our knowledge, this is the first study to demonstrate that ovarian, endometrial, and cervical CAT can be safely and effectively treated using edoxaban. However, there were 2 cases of intraperitoneal hemorrhage and one case of gastrointestinal bleeding due to ovarian cancer carcinomatosis and one case of intestinal bleeding due to radiation colitis in a patient with cervical cancer. These outcomes are tumor-specific features. Carcinomatosis is a common feature of ovarian cancer, whereas irradiation is the standard of care for locally advanced cervical cancer. Whether treatment with DOACs, including edoxaban, is associated with an increased risk of bleeding compared with LMWH or VKA therapy is still unclear. Thus, the possible risks of tumor-specific bleeding need to be considered during therapy especially carcinomatosis of ovarian cancer (**Table S1**) [6,16].

We also investigated the necessity of UFH induction prior to administration of edoxaban because we noted that it had been omitted in many cases in the present study, despite its recommendation by the FDA (**Fig. 2**, **Table 4**, **Fig. S2**). This is probably because initiation of UFH requires in-hospital management with close monitoring of APTT, making it inconvenient in most cases. However, the study data showed that omission of initial UFH therapy did not cause significant increase in the progression of VTE (**Table 4**, **Fig. 2**). However, the backgrounds of the patients in the UFH and single-drug subgroups are different. Compared with the UFH subgroup, the single-drug subgroup had more patients without PE. Nakamura et al. [34] reported similar results in a prospective observational study of the use of edoxaban for the treatment of VTE in a Japanese cohort, approximately 25% of whom were patients with cancer. In that study, 44% of the patients who did not undergo initial UFH treatment did not show increased VTE recurrence. However, most patients with PE or proximal DVT in the study underwent initial UFH therapy. Therefore, the authors concluded that initial UFH is necessary, particularly for PE and proximal DVT. Collectively, we believe that single-drug therapy without initial UFH therapy may be useful for the treatment of patients without severe VTE, such as PE. However, further investigation is needed to provide solid evidence regarding the efficacy and safety of omitting initial UFH therapy for the treatment of patients without severe VTE.

This study has several limitations. First, the retrospective design prevented the elimination of potential confounding biases in the analysis, such as bias in the selection of the treatment method used in each case. Second, we compared the efficacy of edoxaban with that of VKA instead of LMWH. Evidence shows that LMWH is superior to VKA for the treatment of CAT. Unfortunately, LMWH for VTE is not approved in Japan; therefore, it was impossible to compare edoxaban with LMWH in the present study.

In conclusion, this study confirmed that edoxaban is effective and safe for the treatment of gynecological CAT. This result was consistent across types of gynecological cancer.

ACKNOWLEDGEMENTS

Editage assisted with language editing, writing, and proofreading of this article. The authors express their sincere gratitude to them.

SUPPLEMENTARY MATERIALS

Table S1

Details of major bleeding events

Click here to view

Fig. S1

Annual shift in the proportion of patients who received VKA and edoxaban anticoagulants.

Click here to view

Fig. S2

Proportion of patients who received initial UFH during the study period.

Click here to view

REFERENCES

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013;122:1712-23.
PUBMED | CROSSREF
2. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809-15.
PUBMED | CROSSREF
3. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632-4.
PUBMED | CROSSREF
4. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 2014;260:372-7.
PUBMED | CROSSREF
5. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.
PUBMED | CROSSREF
6. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24.
PUBMED | CROSSREF
7. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017-23.
PUBMED | CROSSREF
8. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382:1599-607.
PUBMED | CROSSREF
9. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020;38:496-520.
PUBMED | CROSSREF
10. Khorana AA, Noble S, Lee AY, Soff G, Meyer G, O'Connell C, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1891-4.
PUBMED | CROSSREF

11. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN Guidelines Insights: cancer-associated venous thromboembolic disease, version 2.2018. J Natl Compr Canc Netw 2018;16:1289-303.
PUBMED | CROSSREF
12. Gressel GM, Marcus JZ, Mullen MM, Sinno AK. Direct oral anticoagulant use in gynecologic oncology: a Society of Gynecologic Oncology clinical practice statement. Gynecol Oncol 2021;160:312-21.
PUBMED | CROSSREF
13. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
PUBMED | CROSSREF
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8.
PUBMED | CROSSREF
15. U.S. Food and Drug Administration. Drugs@FDA: FDA-approved drugs [Internet]. Silver Spring, MD: U.S. Food and Drug Administration; [cited 2021 Dec 13]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.
16. Mulder FI, Bosch FT, Young AM, Marshall A, McBane RD 2nd, Zemla TJ, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood 2020;136:1433-41.
PUBMED | CROSSREF
17. Mulder FI, van Es N, Kraaijpoel N, Di Nisio M, Carrier M, Duggal A, et al. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: results from the Hokusai VTE Cancer study. Thromb Res 2020;185:13-9.
PUBMED | CROSSREF
18. Lee JH, Lee JH, Jo KW, Huh JW, Oh YM, Lee JS. Comparison of rivaroxaban and dalteparin for the long-term treatment of venous thromboembolism in patients with gynecologic cancers. J Gynecol Oncol 2020;31:e10.
PUBMED | CROSSREF
19. Shimizu A, Sawada K, Shiomi M, Kawano M, Matsumoto Y, Takiuchi T, et al. Direct oral anticoagulants are effective and safe for the treatment of venous thromboembolism associated with gynecological cancers. Int J Gynaecol Obstet 2019;147:252-7.
PUBMED | CROSSREF
20. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thromb Res 2006;118:555-68.
PUBMED | CROSSREF
21. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007;110:2339-46.
PUBMED | CROSSREF
22. Chew HK, Davies AM, Wun T, Harvey D, Zhou H, White RH. The incidence of venous thromboembolism among patients with primary lung cancer. J Thromb Haemost 2008;6:601-8.
PUBMED | CROSSREF
23. Trugilho IA, Renni MJ, Medeiros GC, Thuler LC, Bergmann A. Incidence and factors associated with venous thromboembolism in women with gynecologic cancer. Thromb Res 2020;185:49-54.
PUBMED | CROSSREF
24. Gade IL, Braekkan SK, Naess IA, Hansen JB, Cannegieter SC, Overvad K, et al. The impact of initial cancer stage on the incidence of venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) Cohort. J Thromb Haemost 2017;15:1567-75.
PUBMED | CROSSREF
25. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation 2012;126:448-54.
PUBMED | CROSSREF
26. Martino MA, Borges E, Williamson E, Siegfried S, Cantor AB, Lancaster J, et al. Pulmonary embolism after major abdominal surgery in gynecologic oncology. Obstet Gynecol 2006;107:666-71.
PUBMED | CROSSREF
27. Einstein MH, Pritts EA, Hartenbach EM. Venous thromboembolism prevention in gynecologic cancer surgery: a systematic review. Gynecol Oncol 2007;105:813-9.
PUBMED | CROSSREF

28. Clarke-Pearson DL, Synan IS, Colemen RE, Hinshaw W, Creasman WT. The natural history of postoperative venous thromboemboli in gynecologic oncology: a prospective study of 382 patients. Am J Obstet Gynecol 1984;148:1051-4.
PUBMED | CROSSREF
29. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer 2013;49:1404-13.
PUBMED | CROSSREF
30. Duska LR, Garrett L, Henretta M, Ferriss JS, Lee L, Horowitz N. When 'never-events' occur despite adherence to clinical guidelines: the case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes. Gynecol Oncol 2010;116:374-7.
PUBMED | CROSSREF
31. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999;78:285-91.
PUBMED | CROSSREF
32. Mahé I, Chidiac J, Bertoletti L, Font C, Trujillo-Santos J, Peris M, et al. The clinical course of venous thromboembolism may differ according to cancer site. Am J Med 2017;130:337-47.
PUBMED | CROSSREF
33. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715-22.
PUBMED | CROSSREF
34. Nakamura M, Yamada N, Asamura T, Shiosakai K, Uchino K. Safety and effectiveness of edoxaban in Japanese venous thromboembolism patients — Final analysis of one-year follow-up data from a Japanese postmarketing observational study (ETNA-VTE-Japan) —. Circ Rep 2020;2:192-202.
PUBMED | CROSSREF