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ORIGINAL ARTICLE

Impact of Anemia on Clinical Outcomes of Patients With Cancer-Associated Isolated Distal Deep Vein Thrombosis Receiving Edoxaban

— Insights From the ONCO DVT Study —

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Background: The ONCO DVT study demonstrated potential benefits of extended edoxaban treatment in patients with isolated distal deep vein thrombosis in terms of thrombotic risk. However, the risk-benefit balance in patients with anemia remains unclear.

Methods and Results: This prespecified subgroup analysis included 601 patients, divided into anemia (n=402) and no-anemia (n=199) groups. The primary endpoint was symptomatic recurrent venous thromboembolism (VTE) or VTE-related death. Anemia was defined as hemoglobin <12 g/dL for women and <13 g/dL for men. In the anemia subgroup, the primary endpoint occurred in 3 (1.5%) and 17 (8.4%) patients in the 12- and 3-month edoxaban treatment groups, respectively (odds ratio [OR] 0.17; 95% confidence interval [CI] 0.05–0.58), compared with 0 and 5 (4.9%) patients, respectively, in the no-anemia subgroup (P interaction=0.997). Major bleeding occurred in 26 (13.1%) and 17 (8.4%) patients with anemia in the 12- and 3-month edoxaban treatment groups, respectively (OR 1.64; 95% CI 0.86–3.14), compared with 2 (2.1%) and 5 (4.9%) patients without anemia (OR 0.67; 95% CI 0.26–1.73; P interaction=0.13).

Conclusions: Regardless of the presence of anemia, edoxaban treatment for 12 months was superior to treatment for 3 months in reducing thrombotic events, whereas the risk of major bleeding did not differ significantly between the 2 treatment groups.

Key Words: Anemia; Bleeding; Cancer-associated thrombosis; Edoxaban; Venous thromboembolism

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication in cancer patients. The risk of VTE in patients with cancer has been reported as being 4- to 7-fold higher than in the general population without cancer.[1] Furthermore, VTE is one of the common causes of death in this population.[2] Current guidelines recommend that patients with cancer-associated VTE should receive prolonged anticoagulation therapy to prevent recurrent VTE.[3–5] However, the therapeutic strategies for isolated distal DVT, which is frequently detected in cancer patients, remain largely unexplored.[6] Recently, the ONCO DVT study, a randomized clinical trial, demonstrated that long-term edoxaban treatment resulted in a

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significantly lower risk of VTE recurrence in patients with cancer and isolated distal DVT compared with short-term edoxaban treatment, suggesting the potential benefit of long-term anticoagulation therapy for these patients.[7]

Bleeding makes long-term anticoagulation therapy challenging. Several risk factors for bleeding during anticoagulant therapy, including anemia, high creatinine levels, a history of bleeding, abnormal renal or liver function, and advanced age, have been identified or validated in patients with VTE.[8–12] Of these factors, anemia is a common characteristic in patients with cancer-associated VTE receiving anticoagulant therapy and is associated with a high risk of bleeding complications and death.[13,14] The therapeutic dilemma between the risk of thrombus and bleeding in patients with cancer and anemia hinders determination of the best treatment algorithm. Accordingly, we conducted a prespecified subgroup analysis of the ONCO DVT study to investigate the safety and efficacy of 12- vs. 3-month edoxaban treatment in patients with cancer-associated isolated distal DVT and anemia.

Methods

Study Design

The ONCO DVT study was an investigator-initiated multicenter open-label adjudicator-blinded superiority randomized clinical trial conducted at 60 institutions in Japan (**Supplementary Appendix 1**). It was designed to compare 12- and 3-month edoxaban treatment regimens in patients with cancer and isolated distal DVT. The trial details have been described elsewhere.[7] Briefly, patients with active cancer and newly diagnosed with isolated distal DVT were randomly assigned in a 1:1 ratio to either the 12- or 3-month edoxaban treatment groups. The trial received approval from the Certified Review Board of Kyoto University and the institutional review boards of all participating institutions (**Supplementary Appendix 2**), and was conducted in compliance with the Declaration of Helsinki and the *Clinical Trials Act of Japan*.

Study Population

Patients with active cancer and isolated DVT were eligible for inclusion in the study. Key exclusion criteria were anticoagulation therapy at the time of diagnosis, a contraindication for edoxaban, PE, and a life prognosis of ≤3 months as determined by the treating physicians.

Following the diagnosis of DVT, edoxaban was administered orally at a fixed dose of 60 mg once daily. For patients with a creatinine clearance of 30–50 mL/min, a body weight of ≤60 kg, or receiving concomitant treatment with potent P-glycoprotein inhibitors, a lower dose of edoxaban (30 mg once daily) was administered.

Definitions

Active cancer was defined as cancer meeting 1 of the following criteria: newly diagnosed within 6 months of randomization; cancer treatment (surgery, chemotherapy, radiotherapy) performed within 6 months of randomization; currently receiving cancer treatment (surgery, chemotherapy, radiotherapy); has recurrence, local invasion, or distant metastases; and hematopoietic malignancy in patients who have not achieved complete remission. Isolated distal DVT was newly diagnosed by whole-leg ultrasound.[15] Anemia was diagnosed based on baseline hemoglobin values and was defined as hemoglobin <12 g/dL in women and <13 g/dL in men.[16] Other definitions are provided in **Supplementary Appendix 3**.

Clinical Endpoints

The primary and major secondary endpoints of this study were consistent with those used in the main analysis. The primary endpoint was a composite of symptomatic recurrent VTE or VTE-related death at 12 months. Symptomatic recurrent VTE was defined as new or newly worsening PE or DVT symptoms, and new thrombi found on imaging tests, or thrombi that had worsened over time compared with the most recent image. Symptomatic VTE recurrence was not determined solely on the basis of the appearance or worsening of thrombus images on imaging without new or worsening symptoms. Similarly, if a patient had a thrombus in an index vein with new symptoms, it was not considered as symptomatic recurrent VTE unless thrombus extension was present. VTE-related death was diagnosed at autopsy, following clinically severe PE or death unexplained by something other than PE. The major secondary endpoint was major bleeding events after 12 months of treatment. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria and included fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding leading to a reduction in hemoglobin levels ≥2 g/dL or requiring transfusions of ≥2 units of whole blood or red cells.[17]

In addition, we assessed all-cause death and all clinically relevant bleeding, including major bleeding and non-major bleeding. Clinically relevant non-major bleeding was defined as clinically overt bleeding (including bleeds detected only using imaging) not meeting the criteria for major bleeding yet leading to ≥1 of the following: physician-guided medical intervention, hospital admission or further treatment for bleeding, or in-person medical examination by a physi-

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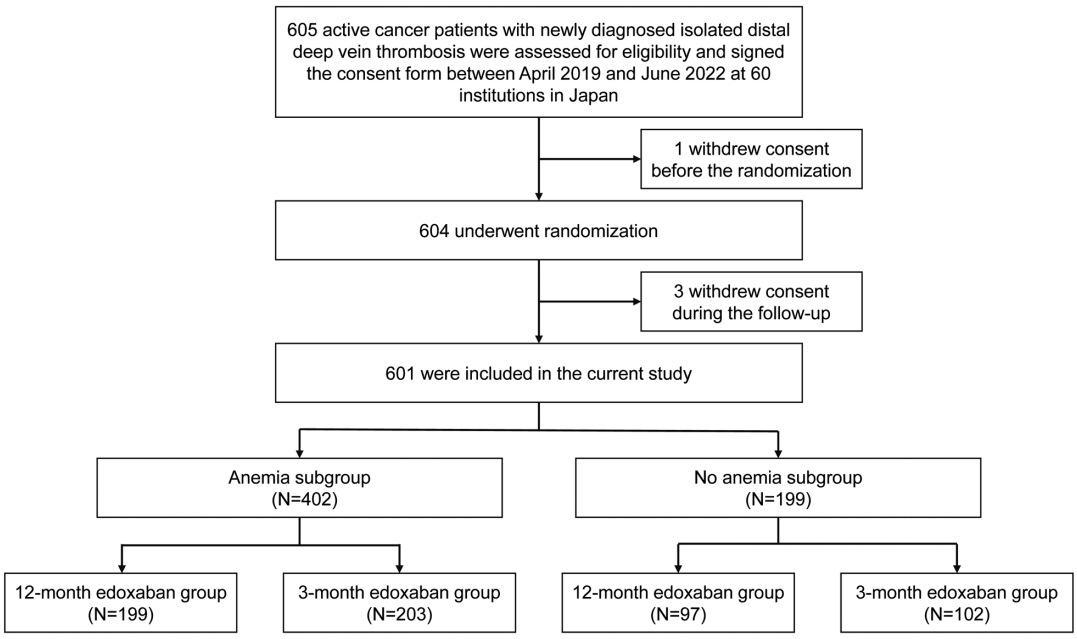


Figure 1. Study flowchart.

cian. Persistent edoxaban discontinuation was defined as the discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason. All patients were assessed for these clinical endpoints after 12 months of treatment.

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean±SD or as the median with interquartile range (IQR) according to their distribution. Categorical variables were compared using the Chi-squared test or Fisher's exact test. Continuous variables were compared using Student's t-test or the Wilcoxon rank-sum test according to their distribution. Cumulative incidence was estimated using the Kaplan-Meier method, and differences between the 12- and 3-month edoxaban treatment groups were compared using the log-rank test. We also calculated odds ratios (OR) with corresponding 95% confidence intervals (CI) for the 12-month edoxaban treatment group relative to the 3-month edoxaban treatment group using logistic regression models. Differences in the effects of 12- relative to 3-month edoxaban treatment regimens were evaluated according to the subgroups using interaction terms in the models. P values are 2-tailed, and statistical significance was set at $P<0.05$. Data were analyzed using SPSS version 29.0.1.0 (IBM SPSS, Inc., Chicago, IL, USA).

Results

Patient Enrollment and Characteristics

From April 2019 to June 2022, 604 patients were randomized. After excluding 3 patients who withdrew consent during follow-up, the present analysis included 601 patients. There were 402 (66.9%) and 199 (33.1%) patients with and without anemia, respectively, in the study cohort (**Figure 1**). Patients with anemia had a lower body mass index (21.9±3.7 vs. 23.7±4.5 kg/m^2; $P<0.001$) and higher platelet levels (25.8±12.7 vs. 23.6±7.2 $\times 10^3/\mu$L; $P=0.007$) than those without anemia (**Table**). Patients with anemia more frequently received the lower dose of edoxaban of 30 mg (78.4% vs. 67.8%; $P=0.007$). The types of cancer are presented in **Supplementary Table 1**. Baseline patient characteristics and the types of cancer were well balanced between the 3- and 12-month edoxaban treatment groups in both the anemia and no-anemia subgroups (**Supplementary Table 2**).

Edoxaban Treatment

In the anemia subgroup, the median duration of edoxaban treatment in the 12- and 3-month treatment groups was 312 and 91 days, respectively. The cumulative 120-day incidence of persistent edoxaban discontinuation was 28.1% in the 12-month treatment group and 88.7% in the 3-month treatment group (**Figure 2**). In the no-anemia subgroup, the median duration of edoxaban treatment in the 12- and 3-month treatment groups was 365 and 95 days, respectively. The cumulative 120-day incidence of persistent edoxaban discontinuation was 15.5% in the 12-month treatment group and 84.3% in the 3-month treatment group.

Primary Endpoint

In the anemia subgroup, the primary endpoint of symptomatic recurrent VTE or VTE-related death occurred in 3 of 199 (1.5%) patients in the 12-month edoxaban treatment group, and in 17 of 203 (8.4%) patients in the 3-month edoxaban treatment group (OR 0.17; 95% CI 0.05–0.58). In the no-anemia subgroup, the primary end-

Table. Patient Characteristics

	Anemia subgroup (n=402)	No anemia subgroup (n=199)	P value
Female sex	286 (71.1)	148 (74.4)	0.44
Age (years)	73 [66–78]	72 [64–77]	0.08
Body mass index (kg/m^2)	21.9±3.7	23.7±4.5	<0.001
Dose of edoxaban			
30 mg	315 (78.4)	135 (67.8)	0.007
60 mg	87 (21.6)	64 (32.2)	
History of VTE	23 (5.7)	10 (5.0)	0.85
Cancer status			
Metastatic	106 (26.4)	41 (20.6)	0.13
ECOG performance status			
0	180 (44.8)	131 (65.8)	<0.001
1	136 (33.8)	45 (22.6)	
≥2	86 (21.4)	23 (11.6)	
History and comorbidities			
Atrial fibrillation	7 (1.7)	2 (1.0)	0.73
History of stroke	19 (4.7)	8 (4.0)	0.84
Hypertension	184 (45.8)	78 (39.7)	0.16
Diabetes	66 (16.4)	35 (17.6)	0.73
CKD	66 (16.4)	25 (12.6)	0.23
Hemoglobin (g/dL)	10.2±1.3	13.4±0.9	<0.001
Platelets (×10^3/μL)	25.8±12.7	23.6±7.2	0.007
Creatinine (mg/dL)	0.73±0.23	0.73±0.20	0.94
eGFR (mL/min/1.73 m^2)	71.9±23.1	68.7±15.5	0.08
AST (IU/L)	21.5 [17.0–29.0]	22.0 [18.0–27.0]	0.23
ALT (IU/L)	16.0 [11.0–26.0]	18.0 [13.0–25.0]	0.94
ALP (IU/L)	190.0 [97.0–267.3]	168.0 [92.5–238.0]	0.12
Medication			
Antiplatelet drugs	31 (7.7)	17 (8.5)	0.75
NSAIDs	84 (20.9)	29 (14.6)	0.08
PPI	144 (35.8)	60 (30.2)	0.17
H_2 blocker	25 (6.2)	9 (4.5)	0.46

Unless indicated otherwise, data are presented as the mean±SD, median [interquartile range], or n (%). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; VTE, venous thromboembolism.

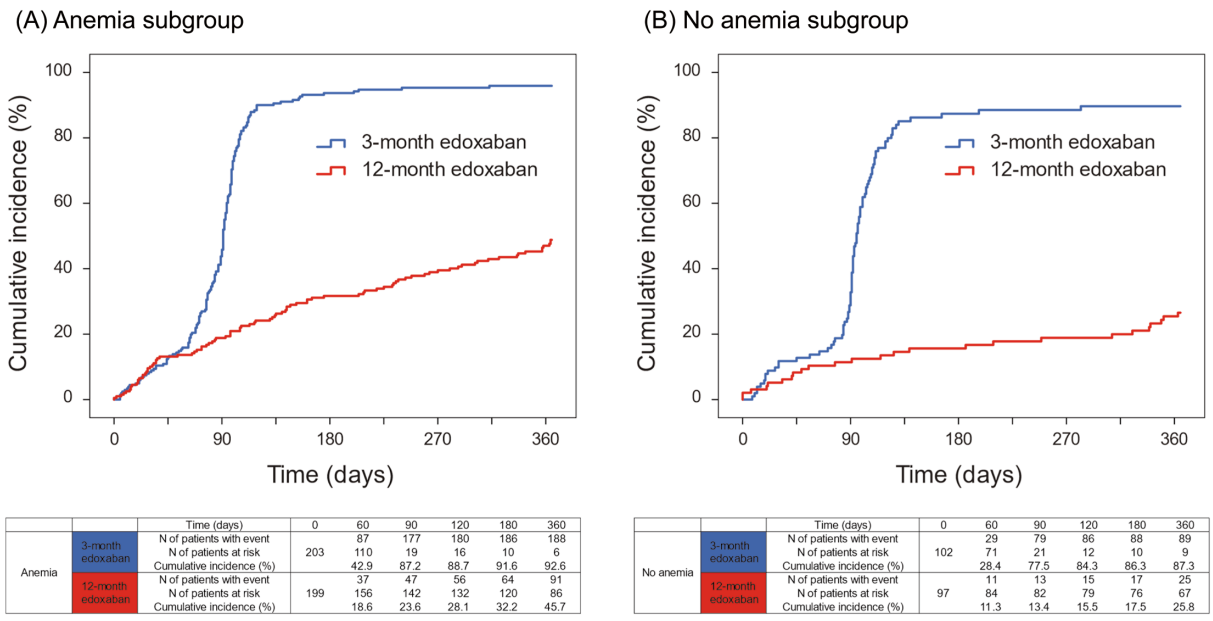
point occurred in 5 of 102 (4.9%) patients in the 3-month edoxaban treatment group; there were no events in the 12-month edoxaban treatment group. There were no VTE-related deaths in either group. The cumulative incidence of the primary endpoint was lower in the 12- than 3-month edoxaban treatment group in both the anemia (log-rank P<0.001) and no-anemia (P=0.02) subgroups (**Figure 3**). No significant interaction was found between the subgroups and the effect of 12-month edoxaban treatment relative to 3-month edoxaban treatment on the primary endpoint (P=0.997; **Figure 4**).

Major Secondary Endpoint

In the anemia subgroup, the major secondary endpoint of major bleeding occurred in 26 of 199 (13.1%) patients in the 12-month edoxaban group and in 17 of 203 (8.4%) patients in the 3-month edoxaban group (OR 1.64; 95% CI 0.86–3.14; **Figure 5**). In the no-anemia subgroup, the major secondary endpoint occurred in 2 of 97 (2.1%) patients in the 12-month edoxaban group and in 5 of 102 (4.9%) patients in the 3-month edoxaban group (OR 0.67; 95% CI 0.26–1.73). The cumulative incidence of major secondary endpoints did not differ significantly between the 3- and 12-month edoxaban treatment groups in either the anemia (log-rank P=0.14) or the no-anemia (log-rank P=0.27) subgroup. No significant interaction was found between the subgroups and the effect of 12-month edoxaban treatment relative to 3-month edoxaban treatment on the major secondary endpoint (P=0.13; **Figure 4**). The sites of major bleeding are presented in **Supplementary Table 3**. The common sites of bleeding were the upper and lower gastrointestinal tract.

Other Secondary Endpoints

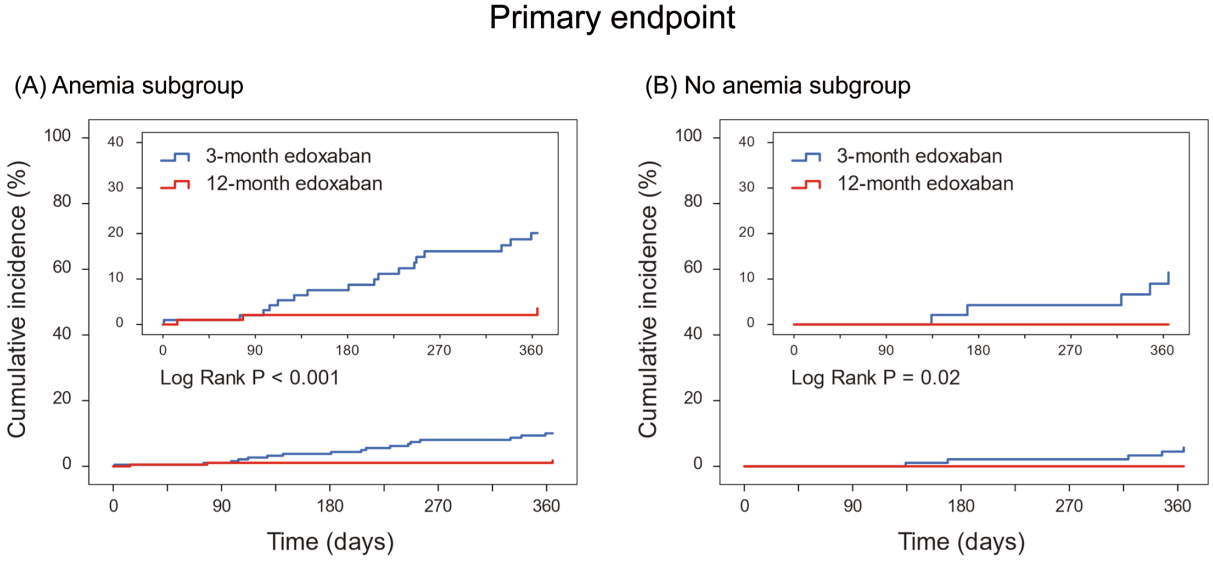
In the anemia subgroup, the cumulative incidence of all clinically relevant bleeding was higher in the 12-month edoxaban treatment group than in the 3-month edoxaban treatment group (log-rank P=0.04), whereas in the no-anemia subgroup the cumulative incidence of all clinically relevant bleeding did not differ significantly between the 2 groups (log-rank P=0.39; **Supplementary Figure 1**). However, there was no significant interaction between the subgroups



		Time (days)	0	60	90	120	180	360
Anemia	3-month edoxaban	N of patients with event		87	177	180	186	188
		N of patients at risk	203	110	19	16	10	6
		Cumulative incidence (%)		42.9	87.2	88.7	91.6	92.6
	12-month edoxaban	N of patients with event		37	47	56	64	91
		N of patients at risk	199	156	142	132	120	86
		Cumulative incidence (%)		18.6	23.6	28.1	32.2	45.7

		Time (days)	0	60	90	120	180	360
No anemia	3-month edoxaban	N of patients with event		29	79	86	88	89
		N of patients at risk	102	71	21	12	10	9
		Cumulative incidence (%)		28.4	77.5	84.3	86.3	87.3
	12-month edoxaban	N of patients with event		11	13	15	17	25
		N of patients at risk	97	84	82	79	76	67
		Cumulative incidence (%)		11.3	13.4	15.5	17.5	25.8

Figure 2. Kaplan-Meier (time-to-event) curves for persistent edoxaban discontinuation comparing 12- and 3-month edoxaban treatment groups in subgroups stratified by anemia status in the 1 year after venous thromboembolism diagnosis. Persistent edoxaban discontinuation was defined as discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason.



		Time (days)	0	60	90	120	180	360
Anemia	3-month edoxaban	N of patients with event		2	4	7	9	17
		N of patients at risk	203	181	176	172	157	132
		Cumulative incidence (%)		1.0	2.0	3.4	4.4	8.4
	12-month edoxaban	N of patients with event		2	2	2	2	3
		N of patients at risk	199	179	173	168	161	137
		Cumulative incidence (%)		1.0	1.0	1.0	1.0	1.5

		Time (days)	0	60	90	120	180	360
No anemia	3-month edoxaban	N of patients with event		0	0	1	2	5
		N of patients at risk	102	98	97	93	89	77
		Cumulative incidence (%)		0.0	0.0	1.0	2.0	4.9
	12-month edoxaban	N of patients with event		0	0	0	0	0
		N of patients at risk	97	94	94	91	89	84
		Cumulative incidence (%)		0.0	0.0	0.0	0.0	0.0

Figure 3. Kaplan-Meier (time-to-event) curves for the primary endpoint comparing the 12- and 3-month edoxaban treatment groups in subgroups stratified by anemia status in the 1 year after deep vein thrombosis diagnosis. The primary endpoint was symptomatic recurrent venous thromboembolism or venous thromboembolism-related death.

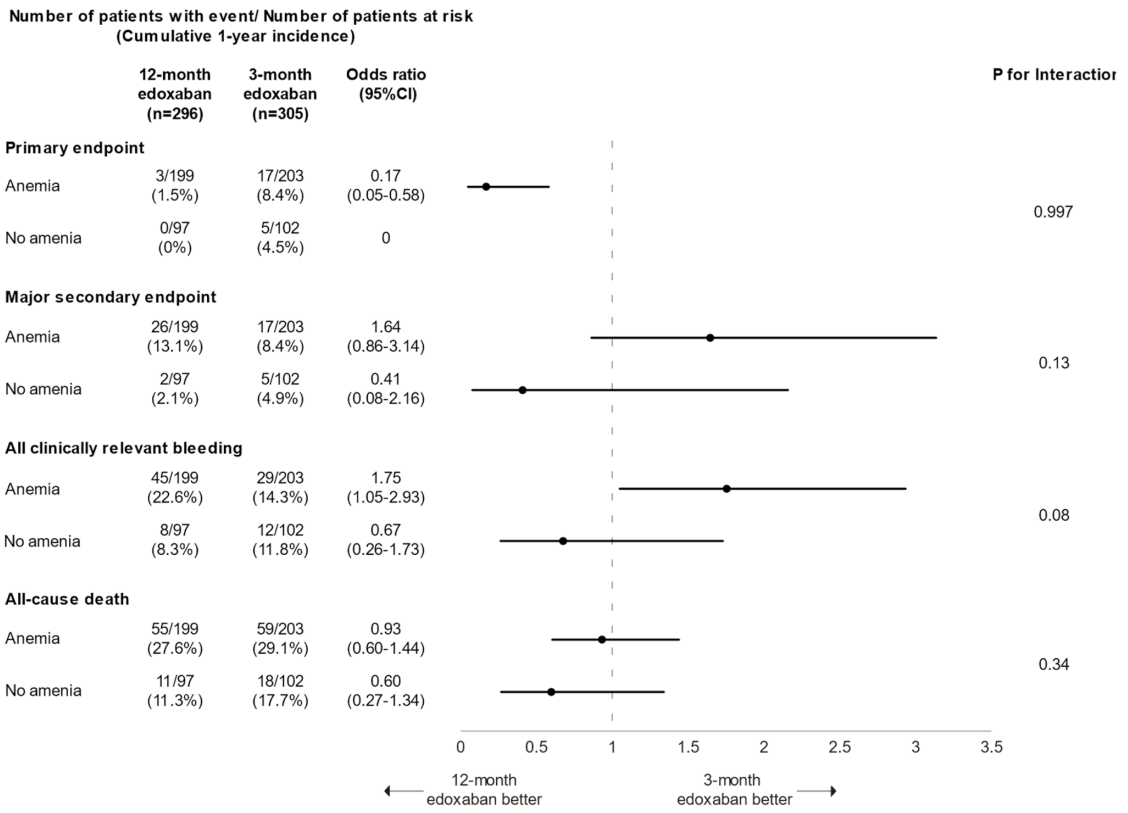


Figure 4. Forest plots for each endpoint. Odds ratios for each endpoint in the 2 groups are provided for the anemia and no anemia subgroups. CI, confidence interval.

and the effect of 12-month edoxaban treatment relative to 3-month edoxaban treatment on all clinically relevant bleeding (P=0.08; **Figure 4**). The cumulative incidence of all-cause death did not differ significantly between the 2 treatment groups in either the anemia (log-rank P=0.80) or no-anemia (log-rank P=0.22) subgroup (**Supplementary Figure 2**). There was no significant interaction between the subgroups and the effect of 12-month edoxaban treatment relative to 3-month edoxaban treatment on all-cause death (P=0.34; **Figure 4**).

Discussion

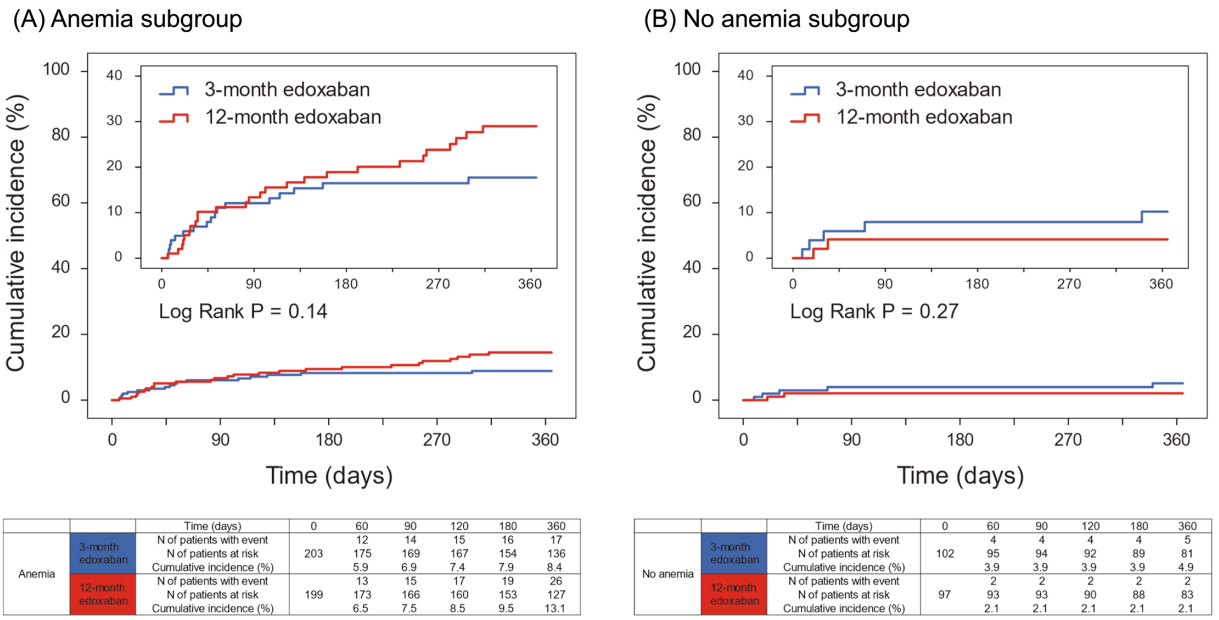
The major findings of this prespecified subgroup analysis of the ONCO DVT study are as follows: (1) 12-month edoxaban treatment is superior to 3-month edoxaban treatment in terms of symptomatic recurrent VTE, regardless of the presence of anemia; (2) there was no statistically significant difference in the risk of major bleeding between the 3- and 12-month treatment groups in patients with and without anemia; (3) the risk of all clinically relevant bleeding was significantly higher in the 12-month treatment group than in the 3-month treatment group in patients with, but not without, anemia.

Anemia and the Risk of Recurrent VTE in Patients With Cancer

As Virchow postulated, the risk of VTE is primarily related to hypercoagulability, altered blood flow, or endothelial vascular lesions.[18] In patients with cancer, the underlying mechanisms of thrombus formation, including activation of the coagulation system, dysregulation of fibrinolytic systems, inflammation, and cytokine production, result in a high prevalence of VTE.[19] Previous studies have reported that cancer-associated VTE is associated with multiple clinical risk factors, including cancer status (cancer site, stage, and time since cancer diagnosis), therapeutic factors (chemotherapy, hormonal therapy, erythropoiesis-stimulating agents, and blood transfusions), and patient-related factors (age, ethnicity, history or family history of VTE, and comorbidities).[20] Among these potential risk factors, anemia, which is a common comorbidity in patients with cancer, has not been considered as a risk factor for VTE.[21] In addition, several previous studies using registry data of VTE patients suggested that the risk of recurrent VTE was similar between patients with and without anemia.[13,14] The present study showed that long-term anticoagulant therapy was superior in terms of preventing VTE recurrence, regardless of the presence of anemia.

Anemia and the Risk of Bleeding in Patients With Cancer

Cancer is well known as a risk factor for bleeding in patients with VTE, and several risk prediction models include cancer as an independent predictor for major bleeding.[22] A recent large observational study of VTE in the direct oral anticoagulants (DOAC) era also reported that patients



		Time (days)	0	60	90	120	180	360
Anemia	3-month edoxaban	N of patients with event		12	14	15	16	17
		N of patients at risk	203	175	169	167	154	136
		Cumulative incidence (%)		5.9	6.9	7.4	7.9	8.4
	12-month edoxaban	N of patients with event		13	15	17	19	26
		N of patients at risk	199	173	166	160	153	127
		Cumulative incidence (%)		6.5	7.5	8.5	9.5	13.1

		Time (days)	0	60	90	120	180	360
No anemia	3-month edoxaban	N of patients with event		4	4	4	4	5
		N of patients at risk	102	95	94	92	89	81
		Cumulative incidence (%)		3.9	3.9	3.9	3.9	4.9
	12-month edoxaban	N of patients with event		2	2	2	2	2
		N of patients at risk	97	93	93	90	88	83
		Cumulative incidence (%)		2.1	2.1	2.1	2.1	2.1

Figure 5. Kaplan-Meier (time-to-event) curves for the major secondary endpoint (major bleeding) comparing the 12- and 3-month edoxaban treatment groups in subgroups stratified by anemia status in the 1 year after deep vein thrombosis diagnosis. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria, comprising fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a reduction in hemoglobin levels ≥2 g/dL or necessitating a transfusion of ≥2 units of whole blood or red cells.

with active cancer had a considerably higher risk of major bleeding than those without cancer, whereby the cumulative incidence of major bleeding in patients with active cancer was reported to be 6.8% at 90 days, 11.5% at 1 year, and 20.4% at 3 years.[23] The higher risk of bleeding may be explained by cancer-related thrombocytopenia, disseminated intravascular coagulation, and elaboration of fibrinolytic factors by tumor cells.[24] Furthermore, DOACs could have significant drug–drug interactions, particularly with inducers and inhibitors of cytochrome P450 3A4 and P-glycoprotein, and inappropriate drug management may have a certain impact on bleeding risk.[25,26]

Anemia is also a well-known risk factor for bleeding in patients with VTE, and the presence of cancer could amplify the risk of bleeding in patients with anemia.[27] Although a previous study demonstrated that DOACs could be a potential first-line treatment option for patients with cancer, there have been few data on bleeding risk in patients with both cancer and anemia.[28] Thus, there could still be considerable uncertainty in the optimal anticoagulation strategies for these patients. The present study showed that there was no statistically significant difference in the risk of major bleeding between short- and long-term anticoagulation therapy, even in patients with anemia. However, long-term anticoagulation therapy in patients with anemia was associated with a significantly higher risk of all clinically relevant bleeding events, which suggests the importance of careful management of patients at high bleeding risk.

Study Limitations

The present study has several limitations. First, the open-label design had the potential to introduce bias, including ascertainment bias. However, all clinical endpoints were adjudicated by members of an independent committee who were blinded to study group assignments. Second, the adherence to edoxaban treatment was relatively low according to the study protocol, especially in patients with anemia. Some of the patients in the 12-month edoxaban treatment group discontinued edoxaban prematurely because of bleeding events or cancer progression. Third, the present subgroup analysis may have been underpowered, and should thus be interpreted as exploratory. Fourth, hemoglobin and medications were only assessed at baseline in the study. Therefore, it was not possible to conduct an analysis that considered the course of anemia. Finally, the present study included patients with various types of cancer, and the treatment for cancer was not standardized. The type of cancer treatment, such as chemotherapy and surgery, may have influenced the present results.[29] The generalizability of the present results should be considered carefully.

Conclusions

Twelve-month edoxaban treatment was superior to 3-month edoxaban treatment in reducing thrombotic events regardless of the presence of anemia, whereas the risk of major bleeding was not significantly different between the 2 treatment groups, regardless of the presence of anemia.

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Disclosures

T.I. is a member of *Circulation Journal*'s Editorial Team. All other authors declare no conflicts of interest.

Author Contributions

Y.Y., T.M., and T.K. conceived and/or designed the study. S.F., Y.Y., N.M., M.U., Y.N., T.T., Y.O., T.N., N.I., K.O., D.S., Y. Tsubata, M.S., A.S., Y.H., Y. Tanabe., R.C., K.T., N.N., K.K., and S.I. collected the data. S.F. and Y.Y. analysed or interpreted the data. S.F. performed the statistical analyses. S.F., Y.Y., T.M., and T.K. prepared the first draft of the manuscript, which was reviewed and edited by all the authors. All authors approved the final version.

IRB Information

The trial received approval from the Certified Review Board of Kyoto University (Reference no. CRB5180002) and the institutional review boards of all participating institutions (**Supplementary Appendix 2**).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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